PB86-118262

Drinking Water Criteria Document for Asbestos (Final Draft)

(U.S.) Environmental Protection Agency
Cincinnati, OH

Mar 85

U.S. Department of Commerce
National Technical Information Service
NTIS

TECHNICAL REPORT DATA

(Please read Instructions on the reverse before completing)

2.

3. RECIPIENT'S ACCESSION NO.
PB86 118262 /AS

SUBTITLE
Drinking Water Criteria Document for
Asbestos

5. REPORT DATE
3/85

6. PERFORMING ORGANIZATION CODE

HOR(S)
Environmental Protection Agency

8. PERFORMING ORGANIZATION REPORT NO.

PERFORMING ORGANIZATION NAME AND ADDRESS

10. PROGRAM ELEMENT NO.

11. CONTRACT/GRANT NO.

12. SPONSORING AGENCY NAME AND ADDRESS
U.S. Environmental Protection Agency
Office of Drinking Water (WH-550)
401 M St., S.W., Washington, D.C. 20460

13. TYPE OF REPORT AND PERIOD COVERED
Scientific review

14. SPONSORING AGENCY CODE

15. SUPPLEMENTARY NOTES

16. ABSTRACT

The Office of Drinking Water (ODW), U.S. Environmental Protection Agency has prepared a Drinking Water Criteria Document on asbestos.
This Criteria Document is an extensive review of the following topics:

- Physical and chemical properties of asbestos
- Toxicokinetics and human exposure to asbestos
- Health Effects of asbestos in humans and animals
- Mechanisms of toxicity of asbestos
- Quantification of toxicological effects of asbestos

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group
Asbestos properties Asbestos exposure Asbestos toxicity Drinking Water		

18. DISTRIBUTION STATEMENT
OPEN

19. SECURITY CLASS *(This Report)*
Non-sensitive

20. SECURITY CLASS *(This page)*
Non-sensitive

21. NO. OF PAGES
176

22. PRICE

United States
Environmental Protection
Agency

FINAL DRAFT
ECAO-CIN-422
March 1985
EPA-600/X-84-199-1

PB86-118262

Research and Development

DRINKING WATER CRITERIA DOCUMENT FOR ASBESTOS

Prepared for

OFFICE OF DRINKING WATER

Prepared by

Environmental Criteria and
Assessment Office
Cincinnati OH 45268

DRAFT: DO NOT CITE OR QUOTE

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LIST OF ABBREVIATIONS

AADI	Adjusted acceptable daily intake
AC	Asbestos cement
ADI	Acceptable daily intake
BaP	Benzo(a)pyrene
bw	Body weight
DNA	Deoxyribonucleic acid
GI	Gastrointestinal
HA	Health advisory
i.p.	Intraperitoneal
IR	Intermediate range
LOAEL	Lowest-observed-adverse-effect level
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
PAH	Polynuclear aromatic hydrocarbons
s.c.	Subcutaneous
SR	Short range
TWA	Time-weighted average

I. SUMMARY

Asbestos is a generic term referring to a family of naturally-occurring hydrated silicates having a fibrous crystalline structure. Only six fibrous silicates are defined as asbestos fibers and are classified under two basic mineral types: serpentine (chrysotile) and amphibole (actinolite, Cunningtonite-grunerite or amosite, anthophyllite, crocidolite and tremolite). Asbestos fibers are widely used for their noncombustible, nonconducting and chemically-resistant properties. However, since chrysotile, amosite, anthophyllite and crocidolite are of primary commercial importance, most data exist for these fiber types. Comparative solubility as defined by acid resistance is chrysotile < < amosite < actinolite < crocidolite < anthophyllite < t[illegible]olite.

Toxicokinetic studies have shown that fibers can penetrate the GI mucosa and thus accumulate in tissues. However, the data indicate that only a small percentage of the fibers ingested are actually involved in penetration and accumulation. Little is known about the metabolism of ingested fibers. The physical and chemical properties of chrysotile and crocidolite fibers have been altered when exposed to simulated gastric juice. It has been demonstrated that ingested fibers are eliminated through the urine and feces (Evans et al., 1973).

Toxic effects following acute, subchronic and chronic oral exposures to asbestos fibers are minimal with no specific target organ defined. In animals, the total extent of effects seen were changes in the mucosal lining cells of the ileum along with changes in the colon, rectum and small intestine. In humans, no specific effects have been defined; however, fibers have been detected in body fluids. In vitro test systems have demonstrated cytotoxic properties of asbestos fibers.

Several animal and human studies have been performed to determine the carcinogenic potential of ingested asbestos fibers. The data obtained from 12 animal bioassays suggest that chronic, high-level ingestion exposures to asbestos fibers failed to produce any definite, reproducible, organ-specific carcinogenic effect. However, many of these studies suffered from an insufficient number of experimental animals and from an inadequate exposure period (i.e., less than lifetime). In male rats ingesting intermediate range fibers at 1% of the diet ad libitum, benign epithelial neoplasms (adenomatous polyps) were observed in the large intestine at the incidence of 9/250 (3.6%) (NTP, 1984).

Ecological studies have been performed on human populations which indicate that cancers of the stomach and pancreas may be associated with the ingestion of asbestos fibers in water. However, these studies are plagued with inherent biases and severe limitations thus weakening the strength of the associations.

Through studies performed, limited both in number and scope, asbestos has not been demonstrated to be either mutagenic or teratogenic in animals following oral exposures. No such studies on humans were located in the available literature.

In an attempt to define a mechanism of asbestos toxicity following oral ingestion, it has been demonstrated that fibers interfere with DNA metabolism in rat-tissues of the GI tract and other organs. Impaired active transport of glucose across membranes and cytotoxic effects have also been demonstrated. Following an evaluation of in vitro tests, it has been concluded that the role of asbestos fibers in the carcinogenesis process in the respiratory tract is one of tumor promotion or cocarcinogenesis versus that of initiation. This is supported by the in vitro tests conducted on PAHs and asbestos fibers.

It has been suggested that asbestos fibers and PAHs may act as cocarcinogens in the causation of lung cancer. This is based on the observations made on the effects of asbestos on BaP transport and metabolism. Asbestos mediates a rapid transport of BaP across cellular membranes and appears to alter BaP metabolism and activity of aryl hydrocarbon hydroxylase in a number of cell types. The relevance of these factors to the ingestion of asbestos has not been established.

The available information on the risk of developing GI cancer associated with the ingestion of asbestos from drinking water is limited. However, using the NTP (1984) study, for a lifetime individual risk of 10^{-5}, 10^{-6} and 10^{-7}, the 95% lower limits of fiber concentration (assuming that the one-hit model is correct) are 7.1×10^7, 7.1×10^6 and 7.1×10^5 f/ℓ, respectively. These results must be viewed in accordance with the estimated levels that would result in increased lifetime cancer risks based on occupational data: 300,000, 30,000 and 3000 f/ℓ for 10^{-5}, 10^{-6} and 10^{-7}, respectively as calculated by the U.S. EPA (1980) or for 10^{-5}, 10^{-6} and 10^{-7} risks for males, 110,000, 11,000 and 1100 f/ℓ, respectively as calculated by the NAS (1983).

II. PHYSICAL AND CHEMICAL PROPERTIES

Asbestos is a generic term referring to a family of naturally-occurring hydrated silicates having a fibrous, crystalline structure which are widely used for their noncombustible, nonconducting and chemically resistant properties. There are many other minerals that when comminuted, produce dust particles that are fibrous; however, most of these other minerals do not possess the above-mentioned properties (Pooley, 1981). The asbestos minerals are divided into two classes based on their chemical and physical properties: the serpentines and amphiboles (Table II-1). The principal types of asbestos are chrysotile, a serpentine mineral, and the amphiboles actinolite, Cunningtonite-grunerite (hereafter referred to as amosite), anthophyllite, crocidolite and tremolite.

The two basic mineral types, serpentine and amphibole, consist of hydrated silicates in a complex crystal system. The chemical composition of the individual types of asbestos are provided in Table II-2. It should be noted, however, that the values obtained from actual chemical analysis of samples might differ slightly from these typical formulae. The individual fibers are discussed in the following sections. Chrysotile is the most abundant form of asbestos. Only chrysotile, amosite, anthophyllite and crocidolite are of commercial importance (IARC, 1976). Additional physical and chemical properties on these four fiber types are provided in Table II-3.

Serpentine Asbestos Fibers

Properties of Chrysotile Asbestos. The crystalline structure of the serpentine form of asbestos differs from that of the amphibole varieties.

TABLE II-1

Classification of Asbestos Minerals*

	CLASS	
	Serpentine	Amphibole
Major types	chrysotile	actinolite, amosite, anthophyllite, crocidolite, tremolite
Basic composition	hydrated magnesium silicate	various silicates of iron, sodium, magnesium and calcium
General physical nature of fiber	pliable, curly	rodlike, straight
General texture of fiber	silky, soft	harsh, stiff
Properties	alkali resistant	acid resistant

*Source: Adapted from Pooley, 1981

In general, the resistance to acid solution is chrysotile << amosite < actinolite < crocidolite < anthophyllite < tremolite (NAS, 1977).

TABLE II-2

Chemical Structure of the Asbestos Fibers[a]

Type	X Site Cations[b]	Y Site Cations[c]	General Chemical Formula
Serpentine - chrysotile	NA	NA	$Mg_3Si_2O_5(OH)_4$
Amphibole - actinolite	Mg,Fe^{2+}	Ca	$Ca_2(Fe^{2+},Mg)_5Si_8O_{22}(OH)_2$
- amosite	Fe^{2+},Mg	Fe^{2+},Mg	$(Fe^{2+},Mg)_7Si_8O_{22}(OH)_2$
- anthophyllite	Mg,Fe^{2+}	Mg,Fe^{2+}	$(Mg,Fe^{2+})_7Si_8O_{22}(OH)_2$
- crocidolite	Fe^{2+},Fe^{3+},Mg	Na	$Na_2(Mg,Fe^{3+},Fe^{2+})Si_8O_{22}(OH)$
- tremolite	Mg,Fe^{2+}	Ca	$Ca_2(Mg,Fe^{2+})_5Si_8O_{22}(OH)_2$

[a] Source: Adapted from Pooley, 1981

[b] X site cations link Si_4O_{11} chains into pairs

[c] Y site cations link the pairs of chains

NA = Not applicable

NOTE: Where cations are written in parentheses without subscripts, a variable composition is indicated with the most predominant species first.

TABLE II-3

General Physical and Chemical Properties of Chrysotile, Amosite, Anthophyllite and Crocidolite*

Property	Chrysotile	Amosite	Anthophyllite	Crocidolite
Mineral association	in altered peridotite adjacent to serpentine and limestone near contact with basic igneous rocks	in crystalline schists, etc. branded ironstones	in crystalline schists and gneisses	iron-rich silicious argillite in quartzose schists branded ironstones
Color	white, grey, green, yellowish	ash grey, greenish or brown	greyish, white brown-grey or green	Lavender, blue, greenish
Hardness (MOHS scale)	2.5-4.0	5.5-6.0	5.5-6.0	4
Specific Gravity	2.55	3.43	2.85-3.1	3.37
Tensile strength (kg/cm²)	31,000	25,000	<5,000	35,000
Young's modulus (kg/cm²)	1.65×10^6	1.65×10^6	--	1.9×10^6
Length	short to long	long	short	short to long
Fusibility	fusible at 1710°C	fusible at 1575°C loses water at moderate temperatures	fusible at 1650°C	fusible at 1335°C

TABLE II-3 (cont.)

Property	Chrysotile	Amosite	Anthophyllite	Crocidolite
Cleavage	010 perfect	210 perfect	210 perfect	210 perfect
Extinction	parallel	parallel	parallel	parallel
Birefringence	moderate first-order	strong second-order	moderate low second-order	weak (masked)
Refractive Index (7α)	1.493-1.553	1.657-1.688	1.578-1.652	1.685-1.698
Refractive Index (7γ)	1.517-1.557	1.657-1.717	1.591-1.676	1.689-1.703
Electric charge	+	-	-	-
Maximum solubility in HCl: % loss in weight	56.00	12.00	2.13	3.14
Maximum solubility in NaOH: % loss in weight	1.03	6.82	1.77	1.20

*Source: Adapted from IARC, 1976

Chrysotile essentially consists of a continuous sheet of silicon-oxygen tetrahedra connected in sandwich fashion to a brucite (magnesium hydroxide) layer in which two of every three hydroxyl groups are replaced by apical oxygens of the silica tetrahedra. The resulting twin-layered sheet (Figure II-1) is strained because of a mismatch between the different dimensions of the brucite and silica sheets. This strain is relieved by curling of the twin-layered sheet with the silica layer innermost (Speil and Leineweber, 1969). Chrysotile fibrils thus consist of scrolls or cylindrical forms having several convolutions. Typically, individual fibrils are long, flexible and curved, and they tend to form bundles that are often curvilinear with splayed ends. Visible chrysotile fibers consist of large aggregates of such bundles weakly associated through hydrogen bonding or physical means (extrafibril solid matter). In transmission electron micrographs, most chrysotile fibrils appear to have a central capillary surrounded by an electron-dense wall. The dimensions of individual chrysotile fibers depend on the extent to which the sample has been "opened" or dissociated into fibrils. In massive form, chrysotile fibers occur in lengths varying from 1-20 mm, with occasional samples as long as 100 mm. After milling, the lengths of typical commercial grade fibrils vary from 1-2 mm and fibril diameters range from 10-80 nm, with mean values of various grades generally falling in the range of 30-38 nm. Although these fibers are small, they have great tensile strength; typical values range from 30,600-44,800 kg/cm^2 for samples 0.3-3.0 cm long. Consequently, chrysotile fibers are frequently used as a reinforcing agent in cement, paper and plastic products. Because of their small diameters and porous surfaces, these fibers also have extremely large surface areas (from ~15-88 m^2/g, depending on sample type and pretreatment). This characteristic is important for filtra-

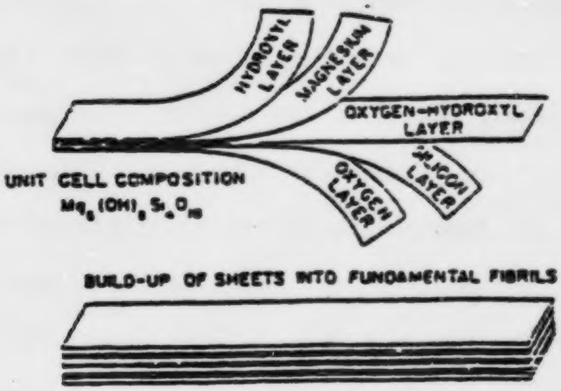
HYDROXYL LAYER
MAGNESIUM LAYER
OXYGEN-HYDROXYL LAYER
SILICON LAYER
OXYGEN LAYER
UNIT CELL COMPOSITION
$Mg_6(OH)_8Si_4O_{10}$
BUILD-UP OF SHEETS INTO FUNDAMENTAL FIBRILS

FIGURE II-1

Fundamental Sheet of Chrysotile

Source: Spell and Leineweber, 1969

tion and reinforcement applications as well as for uses involving aqueous dispersions in the presence of surface active agents such as sodium laurate and dodecylbenzenesulfonate.

Impurities of Chrysotile Asbestos. The empirical formula for chrysotile asbestos is $Mg_3Si_2O_5(OH)_4$. Although, as pointed out previously, this formula may vary slightly from sample to sample, it is nonetheless closely approached by the majority of commercially produced chrysotile fibers. However, a number of impurities have been identified in commercial samples. The most commonly occurring mineral impurities are brucite, chlorite, talc, carbonates, magnetite and quartz; principal metallic impurities include iron, chromium, nickel and manganese. Although virgin chrysotile, in contrast to the amphiboles, is not associated with primary oil or organic impurities, contaminants of this nature have been frequently observed in processed serpentine fibers. These impurities are believed to have resulted through exposure of the fibers to contaminants during manufacturing or storage or through storage in jute or plastic bags.

Reactions and Decomposition. Since the outer surface of a chrysotile fiber is essentially composed of magnesium hydroxide (brucite), chrysotile is highly susceptible to acid attack. Exposure to mineral acids results in the liberation of magnesium ions and the formation of a silicous residue. Chrysotile fibers are almost completely destroyed within 1 hour when placed in 1 N HCl at 95°C. Amphibole fibers are considerably more resistant to mineral acids than are chrysotile fibers (Lindell, 1972). In contrast to the high vulnerability of chrysotile asbestos to acids, however, chrysotile is more resistant to attack by sodium hydroxide than any of the amphibole fibers.

Although asbestos is commonly hailed as a fireproof material and has been widely used as such, all varieties of fibers have been shown to undergo thermal decomposition commencing in the 150-200°C range. Thermal decomposition is accomplished through dehydroxylation and dehydration mechanisms. Under dynamic heating conditions, dehydroxylation occurs at ~650°C, and formation of fosterite and silica is apparent at ~810°C (Speil and Leineweber, 1969). The insulating properties of asbestos are a result of its fibrous structure and the poor thermal conductivity of the individual fibers.

Amphibole Asbestos Fibers

While chrysotile asbestos is considered to be a distinct mineral, the five amphiboles are varieties of other minerals (Zoltai and Stout, 1976). Each of the amphiboles is distinct from the others, differing in both chemical and physical properties. As a commonality, however, they all contain silicon and all form fibers when crushed (U.S. EPA, 1980).

The basic crystal structure of the amphibole minerals is less complicated than that of the serpentine chrysotile. The basic amphibole structure is that of a double silica chain. As is the case with the chrysotile sheets, the silica tetrahedra all point in a common direction. However, in the amphiboles the chains are paired in "back-to-back" fashion, separated by a layer of cations to complement the negative charges of the silica chains (Figure II-2). Magnesium, iron, calcium and sodium have been reported as principal cations in amphibole structure.

All amphibole asbestiform fibers have the same basic crystal structure, double chains of linked tetrahedra that have the unit composition

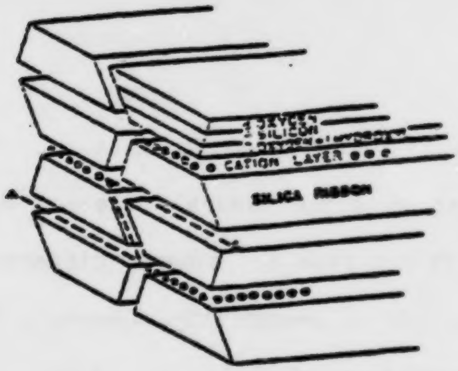
OXYGEN
SILICON
CATION LAYER
SILICA RIBBON
A

FIGURE II-2

Amphibole Structure

Source: Spell and Leineweber, 1969

$(Si_4O_{11})_n$ along the fiber axis. Massive forms of amphibole asbestiform fibers consist of numerous paired chains stacked in an ordered array. The various amphibole asbestiform fibers differ essentially only in the nature of the cations occupying the intraskeletal cation sites. However, the amphibole structure allows great flexibility in cation replacement, and various amphibole asbestiform fibers exhibit a wide range of chemical compositions and physical properties. Only rarely does the composition of a field sample coincide with the assigned theoretical or idealized formula. However, theoretical compositions are used for identifying the various fibers as a matter of convenience.

While the crystal structure of amphiboles is less complex than that of chrysotile, the chemical composition of the asbestiform amphiboles is more complex. Table II-4 provides an indication of the composition and variability of the five amphibole asbestos types.

Properties and common contaminants of specific asbestiform amphiboles are presented in the following discussion.

Properties of Crocidolite Asbestos. Crocidolite, second only to chrysotile in commercial importance among the various asbestiform fibers, is represented by the general chemical formula $Na_2(Mg,Fe^{3+},Fe^{2+})Si_8O_{22}(OH)$. Although amphibole asbestiform fibers are generally straight, splintery and electron opaque, typical crocidolite fiber bundles easily disperse into long, delicate, blue-green fibrils that are elliptical or nearly circular in cross section. Crocidolite fibrils are shorter and thinner than other amphibole asbestiform fibers, but not as small as those of chrysotile.

TABLE II-4

Chemical Composition of Asbestiform Amphiboles*

	Asbestiform Amphibole (range %)				
	Crocidolite	Amosite	Anthophyllite	Actinolite	Tremolite
SiO_2	49-53	49-53	56-58	51-56	55-60
MgO	0-3	1-7	28-34	15-20	21-26
FeO	13-20	34-44	3-12	5-15	0-4
Fe_2O_3	17-20	---	---	0-3	0-0.5
Al_2O_3	0.0.2	---	0.5-1.5	1.5-3	0-2.5
CaO	0.3-2.7	---	---	10-12	11-13
K_2O	0-0.4	0-0.4	---	0-0.5	0-0.6
Na_2O	4.0-8.5	trace	---	0.5-1.5	0-1.5
H_2O	2.5-4.5	2.5-4.5	1.0-6.0	1.5-2.5	0.5-2.5

*Source: Speil and Leineweber, 1969

However, the dimension and coarseness of crocidolite vary in different geographic locations (Wagner et al., 1960). The modal width and length of the Union Internacional Contre le Cancer (UICC) standard reference samples of crocidolite ultrasonically dispersed in water are 0.13 μm and ~0.6 μm, respectively. Crocidolite fibers are the strongest of the amphiboles, with a tensile strength of ~30,000 kg/cm² for a "typical" sample. The surface area of each of the five varieties of amphibole asbestos fibers is substantially less than that of chrysotile. Crocidolite fibers generally have surface areas in the 5-15 m²/g range, depending on the nature of pretreatment of the sample. In distilled water at pH 7.4., the surface charge (zeta potential) of amphibole fibrils is negative and smaller in magnitude than the positive charge on chrysotile fibrils. The complementary nature of these properties is utilized advantageously in the asbestos cement industry by blending crocidolite and chrysotile fibrils to achieve optimal sedimentation and filtration rates. In comparison with other amphiboles or chrysotile, crocidolite has relatively poor resistance to heat, but its fibers are used extensively in applications requiring good resistance to acids or sea water. Crocidolite fibers have fair to good flexibility, fair spinnability, and a texture ranging from soft to harsh. Unlike chrysotile, crocidolite is usually associated with organic impurities, including low levels of carcinogenic, PAHs such as BaP.

Properties of Amosite Asbestos. Amosite is a fibrous, monoclinic form of the amphibole grunerite, which ranks next to crocidolite in commercial importance. The general chemical formula for amosite is $(Fe^{2+},Mg)_7Si_8O_{22}(OH)_2$; the Fe^{2+} to Mg ratio varies but typically is ~5:2. Amosite fibrils are generally larger than those of crocidolite but smaller than particles of anthophyllite. Most amosite fibrils have straight edges and characteristic right-angle fiber axis terminations. The modal width and length of UICC standard reference amosite ultrasonically dispersed in water are 0.14 μm and ~1.4 μm, respectively. Amosite fibril bundles have roughly half the tensile strength attributed to crocidolite fibers and are less resistant to chemical attack than any of the other amphibole asbestiform fibers except actinolite. Unlike crocidolite, however, amosite has good heat resistance, and ~84% of the reported U.S. consumption of this fiber is used for thermal insulation. Like other amphibole asbestiform fibers, virgin amosite characteristically contains small quantities of extractable organic matter, including traces of the carcinogen BaP.

Properties of Anthophyllite Asbestos. Anthophyllite is a relatively rare, fibrous, orthorhombic, magnesium-iron amphibole that is currently produced in commercial quantities only in the Paakkola area of Finland. Its general chemical formula is $(Mg,Fe^{2+})_7Si_8O_{22}(OH)_2$, where the Mg to Fe^{2+} ratio is variable but large with Mg being the predominant species. Typically, anthophyllite fibrils are more massive than other common forms of asbestos. The modal width and length of the UICC standard reference material ultrasonically dispersed in water are 0.18 μm and ~5.1 μm, respectively. The tensile strength of anthophyllite fibers is inferior to that of all the other forms of asbestos except tremolite, and its harsh texture, short length and brittle nature limit its spinnability. However, anthophyllite fibers have good resistance to heat and are moderately attractive as a filter medium.

Properties of Actinolite and Tremolite Asbestos. The remaining types of common asbestiform fibers include tremolite, the monoclinic calcium-magnesium amphibole, and its predominantly iron-substituted derivative, actinolite. Tremolite has the general chemical formula $Ca_2(Mg,Fe^{2+})_5Si_8O_{22}(OH)_2$. The formula for actinolite is similar except that part of the magnesium content is preferentially replaced by iron(II) cations: $Ca_2(Fe^{2+},Mg)_5Si_8O_{22}(OH)_2$. Tremolite forms fibrils more massive than those of either crocidolite or amosite, but comparable to those of anthophyllite. In electron micrographs these fibrils exhibit characteristic irregularities in edges and ends. Although tremolite fibrils are the lowest in tensile strength of all the common types of asbestos, they exhibit good resistance to chemical attack by both acids and alkalis. The tensile strength of actinolite is ~4 times greater than that of tremolite, but it is the most vulnerable of all the amphibole asbestiform fibers to attack by acids and alkalis. Currently, neither actinolite nor tremolite is produced commercially, and little information exists concerning their mining activities, uses, or physical and chemical properties; however, Canadian chrysotile contains small amounts of tremolite (Craighead and Mossman, 1982).

Summary

Only six fibrous silicates are classified as asbestos fibers based on specific physical properties including heat resistance and the ability to be woven (Pooley, 1981). These fibers are classed under two basic mineral types: serpentine (chrysotile fiber) and amphibole (actinolite, amosite, anthophyllite, crocidolite and tremolite fibers). Only chrysotile, amosite, anthophyllite and crocidolite are of commercial importance; thus, most data exist for these fibers. Chemical composition of the individual fibers will vary with point of origin; however, the serpentine chrysotile is most distinct from the five amphibole asbestos fibers. Chrysotile is a hydrated magnesium silicate whereas the amphiboles are silicates of iron, sodium, magnesium and calcium. Comparative solubility as defined by resistance to acid solution is chrysotile << amosite < actinolite < crocidolite < anthophyllite < tremolite. Pertinent physical and chemical properties for the four fibers of commercial importance are summarized in Table II-3.

III. TOXICOKINETICS

Absorption and Distribution

Ingestion of Asbestos. Exposure to asbestos fibers might occur through the ingestion of drinking water, recreational water, foods and beverages contaminated with asbestiform fibers, or through the swallowing of such fibers cleared from the respiratory passages by mucocilliary activity. Thus, asbestos might ultimately reach the GI tract either directly by ingestion or indirectly from the lungs through the vascular or lymphatic systems. A vital question in the determination of the significance of ingestion to the potential pathogenicity of asbestos is whether asbestos actually migrates across the intestinal mocosa and from there enters the blood or lymphatic circulation -- a condition that would permit both the embedding of fibers in the intestinal wall and transport to other organs and tissues of the body. Such movement of fibers is a likely precursor of carcinogenesis following the ingestion of asbestos (Cook, 1983). The question of GI migration has been studied by a number of independent researchers. Cook (1983) recently reviewed the literature and critically evaluated each study to assess the significance of their findings. Biological, analytical, mineralogical and kinetic factors were considered.

It is obvious from Table III-1 that the preponderance of evidence seems to be in favor of transmigration of asbestos through the GI wall. In addition, a number of investigators have addressed this issue by displaying evidence of penetration by ingested particles other than asbestos, mineral or synthetic fibers; thus, demonstrating the possibility of such movement and subsequent tissue accumulation.

TABLE III-1

Summary of Studies on Fiber Penetration of the Gastrointestinal Mucosa[a]

Evidence For/ Against	Species	No. Examined	Fiber Type	Fiber Dose Characterization	Exposure Duration	Tissues Analyzed[b]	Tissue Preparation Method[c]	Microscope Technique	Detection Limit Reported	Positive/ Negative Control Samples	Reference
+	Rat	3	chrysotile	no characterization, 6% diet	3 mo	colon (+) mesenteric nodes (-) spleen (-)	thin sections	TEM	no, qualitative	no/no	Westlake et al., 1965
+	Rat	5 5 5	chrysotile chrysotile control	9.6×10^6 fibers 94×10^6 fibers no fibers	stomach injection	blood (+) omentum (+) brain (+) lung (-) spleen (-) heart (-)	bulk, soluene, centr HTA, drop HTA, drop	TEM	no	no/contaminated	Cunningham and Pontefract, 1973; Pontefract and Cunningham, 1973
-	Rat	10 5	chrysotile control	no characterization, 5% diet no fibers	21 mo	intestine (-) mesentery (-) other organs (-)	bulk, bleach, centr, wash, drop	TEM	incomplete	no/contaminated	Gross et al., 1974
	Rat	10 10 5	amosite tailings control	no characterization, 400 mg no fibers	single gavage	intestine (-) mesentery (-) lung (?) kidney (-)	bulk, bleach, centr, wash, drop	TEM	no	no/yes	
	Rat	10 10 10	amosite tailings control	no characterization, 10, 20% diet no fibers	6 days	intestine (-) mesentery (?) lung (-) kidney (-)	bulk, bleach, centr, wash, drop	TEM	no	no/yes	
-	Rat	2 2 2 2	chrysotile crocidolite amosite control	UICC 250 mg/wk no fibers	1 yr + 1 mo free from exposure	GI tract (-)	bulk, HTA, acid, filt	SEM	incomplete, semiqualitative	no/yes	Bolton and Davis, 1976

TABLE III-1 (cont.)

Evi-dence For/Against	Species	No. Exam-ined	Fiber Type	Fiber Dose Characterization	Exposure Duration	Tissues Analyzed[b]	Tissue Preparation Method[c]	Microscope Technique	Detection Limit Reported	Positive/Negative Control Samples	Reference
+	Rat	10 10	chrysotile control	fiber size only, 1% diet no fibers	6 wk	blood (?) omentum (+) lung (+) kidney (+) liver ( ) brain (+)	bulk, LTA, acid, filt, LTA, drop	TEM	no	no/contaminated (less than 1973)	Cunningham et al., 1977
+	Rat	5 2	amosite control	UICC, 0.1 mg saline	1 hr in isolated jejunum segment	epithelial surface penetration (+)	SEM preparation	SEM	qualitative	no/yes	Storeygard and Brown, 1977
-	Human	282	asbestos bodies	no characterization		lung (+)	bulk, LTA	OM	incomplete	yes/no	Auerbach et al., 1977
+	Human	8 8	amphibole control	10^8 fibers/ℓ in water $<10^6$ fibers/ℓ in water	variable by subject	urine (+)	bulk, filt, LTA, filt, c-coat, wick	TEM	-10 fibers/mℓ	yes/yes	Cook and Olson, 1979
+	Baboon neonate	1 1	chrysotile control	ca. $3x10^{10}$ fibers in milk no fibers	9-day period	kidney (+) liver (-) spleen (-)	bulk, LTA, filt, LTA filt, drop	TEM	-80 fibers/mg	no/yes	Patel-Mandlik et al., 1979
+	Baboon	1	chrysotile	UICC, 120 kg pregavage	4 days gavage	urine (+)	bulk, filt, LTA, filt, LTA, drop	TEM	$5x10^3$ fibers/mℓ	no/yes	Hallenbeck and Patel-Mandlik, 1979
+	Human	53[d]	amphibole chrysotile	10^8 fibers/ℓ in water none in water	variable by subject	liver (+) lung (+) jejunum (+)	bulk, KOH, centr HTA, drop	TEM	30 fibers/mg	yes/yes	Carter and Taylor, 1980
+	Rat	5 5 15 8 2	chrysotile crocidolite chrysotile chrysotile control	UICC, -10^{11} fibers UICC, -10^{10} fibers NIEHS 10^{11} to 10^{10} fibers NIEHS 10^{10} to 10^{11} fibers no fibers	single gavage single gavage diet <1-12 days diet <1-12 days 	lymph fluid (+) lymph fluid (+) lymph fluid (+) lymph fluid (+) lymph fluid (+)	bulk, digestion, filt, c-coat, wick	TEM	incomplete	no/yes	Sebastien et al., 1980

TABLE III-1 (cont.)

Evidence For/ Against	Species	No. Examined	Fiber Type	Fiber Dose Characterization	Exposure Duration	Tissues Analyzed[b]	Tissue Preparation Method[c]	Microscope Technique	Detection Limit Reported	Positive/ Negative Control Samples	Reference
+	Rat	10	chrysotile	UICC, 10% diet	2 yr	colon (+)	thin, 20 μm, HTA	TEM	no	no/yes	Donham et al., 1980
		10	cellulose	cellulose fibers		colon (-)					
		6	control	no fibers		colon (-)					
+	Baboon newborn	1	chrysotile	UICC, 3×10^{10} fibers	9-day period	kidney cortex (+) lymph nodes (+) spleen (+) colon (+) esophagus (+) kidney medula (+) other sites (-)	bulk, LTA, filt, LTA, drop		~80 fibers/ mg	no/yes	Patel-Mandlik and Millette, 1980
		1	control	no fibers							
+	Human	34	chrysotile	none in drinking water	unknown	urine (+)[e]	bulk, filt, LTA, filt, c-coat, wick	TEM	~10 fibers/mℓ	no/yes	Cook and Longrie, 1981
+	Human	1	attapulgite	5 g/day	drug, 6 mo	urine (+)	bulk, undefined	TEM	no	no/yes	Bignon et al., 1981
-	Baboon	1	chrysotile	NIEHS, 800 mg	gavage, 8 times	urine (-) blood (-)	bulk, filt, LTA, acetone, drop	TEM	~4×10^3 f/mℓ ~4×10^4 f/mℓ	yes/yes	Hallenbeck et al., 1981
			crocidolite	NIEHS, 800 mg		tissues (-)	bulk, KOH, filt, LTA, acetone drop		200 f/mg		
		1	control	no fibers							
+	Fish	2	amphibole	ca. 10^6 fibers/ℓ	lifetime, water and possibly diet	kidney (+)[f] liver (+) muscle (+)	bulk, LTA, filt, c-coat, wick	TEM	1-10 f/mg	no/yes	Batterman and Cook, 1981
		1	amphibole	ca. 10^4 fibers/ℓ							
		2	chrysotile	unknown							

TABLE III-1 (cont.)

Evidence For/ Against	Species	No. Examined	Fiber Type	Fiber Dose Characterization	Exposure Duration	Tissues Analyzed[b]	Tissue Preparation Method[c]	Microscope Technique	Detection Limit Reported	Positive/ Negative Control Samples	Reference
-	Rat	13	chrysotile	UICC, 250 mg/wk	>20 mo	9 sites (-)[g]	bulk, LTA, acid, filt	SEM	incomplete	no/no	Bolton et al., 1982
		12	amosite								
		13	crocidolite								

[a]Source: Cook, 1983

[b]Positive or negative for fibers

[c]Preparation method steps: thin - removal of a thin tissue section for examination; bulk - processing a large volume of tissue to isolate and concentrate the inorganic particles; HTA - high temperature ashing; LTA - low temperature ashing; KOH, bleach, Soluene - chemicals for digestion of tissue to remove organic matrix; acid - use of dilute acid to dissolve the nonsilicate portion of the ash; centr - centrifugation to isolate particles from suspension, filt - membrane filtration to remove particles from suspension usually prior to TEM grid preparation; c-coat, wick - preparation of a TEM grid by dissolving a piece of carbon-coated membrane filter by solvent wicking action to leave the particles embedded in the carbon film suspended on the grid; drop - preparation of TEM grid by evaporation of a small drop of a particle suspension on a carbon-coated TEM grid.

[d]Samples were pooled as an exposure group (32 subjects exposed to amphibole fibers in drinking water) and a control group (no amphibole fibers in drinking water).

[e]Number of fibers in urine exceeded number in blank for each urine sample.

[f]Amphibole concentrations in replicate preparations of tissues were found to fit a dose-response relationship with concentrations greatest in kidney and very low in muscle tissue.

[g]Some fibers were found in tissues (no comparison to blank samples) but concluded to be insignificant on the basis of a lack of preferential retention in any specific tissue, particularly the mesenteric lymphatic tissues. The authors also indicated difficulty in identifying fine fibers (<0.1 μm diameter) with the SEM.

LeFevre et al. (1978) observed that mice, after drinking water suspensions of 2 μm diameter latex spheres for 2 months, had the latex particles accumulated in macrophages in intestinal Peyer's patches. Latex particles of 0.22 μm were reported by Sanders and Ashworth (1960) to migrate from the stomachs of rats to lymphatics of the mucosa, as well as to the liver and kidney tissues. Much larger particles of silica, in the form of opal phytoliths from plants, have been observed in digested mesenteric lymph node and kidney tissue from sheep that eat cereal chaff and grains (Nottle, 1977).

Volkheimer (1972) observed that particles of micrometer proportions are regularly incorporated in the GI tract by persorption. During persorption, corpuscular particles are passed between epithelial cells into the subepithelial layer where they are transported by portal circulation or chyle. Volkheimer (1974) later investigated the process of persorption in rats, rabbits, chickens, guinea pigs, dogs and pigs. Animals were administered suspensions of particulates by intragastric or rectal tube to determine the mechanisms of persorption. These particulates included starch granules, cellulose particles, powdered rabbit hair, charcoal, pollen, spores, polyvinyl globules and silicates. Animals were sacrificed at various times (not specified) after particulate administration. Upon histological examination of the small intestine, particles were found between epithelial cells, in the subepithelial layer of the mucosa and in the lumen of the lymph vessels. Two hours after dogs were given the particulate suspension, persorbed particles were found in body fluids (specific type not reported), chyle (from the thoracic duct), blood, bile and urinary bladder. The majority of the particles that were persorbed ranged between 15 and 75 μm in diameter. A silicate of 150 μm was reportedly found in the lymph of one animal. Volkheimer (1974) did not specify, however, the number of animals per species used in the study, the precise time of sacrifice following exposure, whether or not control animals were used, or how the particulates were identified in the histological samples. The concentration and volume of the particulate suspension were also not reported by the author. Despite these shortcomings, the study does provide some information as to the mechanism of persorption and the distribution of persorbed particles.

Schreiber (1974) reported that dyed cellulose fibers, administered orally in the form of specially stained plant food, were found in both the blood and urine of human subjects. The cellulose fibers were present in the urine several weeks after ingestion.

Although such data on a variety of particulates support the theory of GI migration of asbestos fibers, such inferences need not be made in light of the evidence presented in Table III-1. Cook (1983) noted that based on these studies it would be difficult to conclude that asbestos fibers do not cross the GI barrier. The weight of evidence is by far, in favor of the occurrence of this event. However, as Cook points out, it is perhaps more important to consider the fraction of ingested fibers that may be involved in GI migration rather than the probability of the migration actually occurring. Unfortunately, little information is available to estimate the percentage of fibers involved in actual migration. Sebastien et al. (1980) estimated that a maximum of 10^{-4} to 10^{-7} times the number of chrysotile or crocidolite fibers introduced to the stomach appeared in the lymph fluid of rats (Cook, 1983). Analyzing human urine, Cook and Olson (1979) detected $\sim 10^{-3}$ of the concentration present in the subject's drinking water that had been consumed up to 20 years before the study. Unfortunately, these data are limited in that neither the lymph fluid nor the urine can account for all fibers that may move across the GI mucosa. However, the data do indicate that a small percentage of fibers ingested are actually involved in penetration and consequently in tissue accumulation and increased cancer risk (Cook, 1983).

Injection of Asbestos. The applicability of injection experiments to human risk assessment has been viewed with skepticism. Such injections do simulate common human exposure conditions (i.e., small amounts found in drugs in countries that permit the filtering of drugs through asbestos pads during production processes). However, the primary value is that injection of asbestos permits more controlled conditions than are possible in ingestion or inhalation experiments. Thus, these studies need not be disregarded solely on the basis of route of exposure.

Cunningham and Pontefract (1973) detected fibers in beverages (beer, wine and soft drinks) and were interested in determining if such fibers consumed orally can pass through the intestinal wall and enter the bloodstream. A stock solution was made to contain fibers the same length as those found in beverages (0.5-2 μ) and determined to contain 9.4×10^6 fibers/ℓ. An aliquot (assumed to be 350 mℓ) was then administered intragastrically to rats (number, species and sex not known). Asbestos fibers were found to accumulate in the omentum surrounding the small intestine, brain and lungs. According to the authors, counts could not be made on the liver and kidneys.

Roe et al. (1967) injected 20 female CBA mice subcutaneously in two sites. Each injection contained 10 mg fiber suspended in 0.4 mℓ saline. Each animal received three injections into each flank. The flank was chosen as a site well distant from the thorax. Three fiber types -- crocidolite, amosite and chrysotile -- were tested to study their distribution. All three fiber types were found in the submesothelial tissues of the thorax and abdomen. In addition, extensive inflammatory changes and some sarcomas developed at the injection sites, while transport of fibers to submesothelial tissues culminated in mesothelioma.

Chrysotile dust injected intraperitoneally into rats was found to migrate into the peribronchial and perivascular tissues of the lung and was observed in alveolar epithelial cells (Karacharova et al., 1969). In another study using i.p. injection as the mode of exposure, UICC standard amosite, anthophyllite or crocidolite was administered to female Wistar rats as a regimen of 20 mg/week for 5 weeks (Friedrichs et al., 1971). The animals were sacrificed 4 months after the initial injection and subjected to histological examination. Fibers of varying lengths were observed in granulomas, the shorter fibers being generally intracellular and the longer fibers extracellular. Transport of fibers from the site of injection was found to be somewhat dependent upon fiber length; shorter fibers are noted to be more readily transported than longer ones.

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Kanazawa et al. (1970) investigated the migration of asbestiform fibers in mice following s.c. injection. Improved staining, microincineration and electron microscopy techniques led to a confirmation of lymphatic transport but demonstrated that the amount transported was less than formerly believed. Fibers accumulated in lymphoid tissues (primarily axillary lymph nodes) but were also concentrated in inguinal, mediastinal and lumbar nodes. Some fibers were found in the spleen and in nonlymphoid organs such as the liver, kidneys and brain, suggesting that some fibers had entered the bloodstream. Most asbestos fibers probably travel inside macrophages, although some larger fibers may be free in the lymph or blood (Kanazawa et al., 1970). Selective transport of fibers to the subserosal tissue, as suggested in Roe et al. (1967), was not supported by this study.

The transport of chrysotile fibers from the maternal blood across the placenta to the fetus was reported by Cunningham and Pontefract (1974). Dosages of 1-3 mg (1 mg/mℓ of water) were injected into the femoral vein of female Wistar rats at 2-day intervals from days 10-14 of gestation. Total dose varied from 4-12 mg of asbestos. The fetuses were removed by Caesarean section the day before parturition in a manner that prevented cross-contamination from the mother; the livers and lungs were then analyzed by electron microscopy. Asbestos fibers were found to cross the placenta but the extent of this occurrence was highly variable. The livers and lungs analyzed were selected at random and thus could have come from different fetuses in the same uterus. In the first experiment, the highest number of fibers found in fetal liver and lungs came from a dam administered four 3 mg injections (total dose = 12 mg). Numbers of fibers found in liver and lungs were 27.03×10^{6} f/g and 139.97×10^{6} f/g, respectively. In a second experiment, the highest number of fibers found in fetal liver and lungs came from a dam administered five 2 mg injections (total dose = 10 mg). Numbers of fibers found in the liver and lungs were 100.12×10^{6} f/g and 2.90×10^{6} f/g, respectively.

Interspecies Variability of Response to Asbestos. Zaidi (1974) emphasized the need for investigators to use suitable animal models to correlate results with effects in humans. He cited major differences between the stomachs of rats and humans as an example and suggested that the dog or the guinea pig would be a more suitable model. Zaidi discussed the possible role of the mucous barrier in preventing absorption of asbestos in the GI tract, and noted that high levels of mucous production, either as a species-specific phenomenon or as a result of individual differences in feeding, could influence the results in studies of uptake. It was suggested that destruction of the mucous barrier (e.g., by the use of drugs) might allow greater absorption of asbestos from the GI tract, leading to a greater neoplastic response.

Bioaccumulation/Retention

Patel-Mandlik and Millette (1983) designed a study to determine if penetration, migration and retention occur in animals chronically exposed to ingested asbestos. Sprague-Dawley rats exposed to asbestos fibers *in utero* were given 50 mg/kg intermediate range (IR) chrysotile asbestos by gavage 2 times/week. This was done until natural death or sacrifice. The rats were then divided into groups by age at death: 0-200, 200-400, 400-600 and 600-800 days. Random samples (5/group) were taken and kidneys were analyzed for asbestos fibers. Four control rats (1/age group) were chosen to represent asbestos levels in control tissues. Fibers were shown to pass across the GI wall. In addition, a rise in fiber levels was detected in tissues from group 1 to group 3. However, levels dropped in group 4. The authors state that this drop could be due to time-related biological causes of low fiber recovery such as degradation of fibers beyond TEM identity and elimination of fibers in feces and urine. Thus, accumulation is demonstrated.

Metabolism

Little information is available on the metabolism of ingested asbestos. As noted in the Section on Absorption and Distribution, fiber penetration into and migration across the gut wall occurs. Seshan (1983) demonstrated that physical and chemical properties of chrysotile change substantially with <1-hour exposure to simulated gastric juice (equivalent to 1N HCl). The Zeta potential was changed from positive to negative; Mg++ ions were leached from chrysotile; the refractive index of the fiber changed; and long range structural order was lost with a concomitant reduction in X-ray diffraction signal. Surface properties were altered with N_2 adsorption being doubled and dye adsorption greatly increased. No such changes were seen with crocidolite.

Lukens (1978a,b) performed immunochemical studies aimed at development of a method for determination of asbestos in environmental samples. His results indicated that, unlike normal control globulins, experimental globulins obtained from rabbits injected with bovine serum albumin-coated asbestos were found to bind with asbestos.

Elimination

As discussed in the Section on Absorption and Distribution, recent studies have resulted in contradictory conclusions regarding recovery of ingested asbestos fibers in urine of exposed test animals. Hallenbeck and Patel-Mandlik (1979) indicated that chrysotile fibers orally administered to baboons may be recovered in the urine.

Cook and Olson (1979) conducted a study in which human urine sediment examined by transmission electron microscopy, contained amphibole fibers that the authors contend were clearly associated with the type of drinking water ingested by the subjects. Urine samples were obtained from residents of Duluth, MN drinking unfiltered water from Lake Superior. Ingestion of filtered water resulted eventually in the disappearance of amphibole fibers in urine. Cook and Olson (1979) report that their data provide the first direct evidence for the passage of mineral fibers through the human GI mucosa.

Boatman (1983) analyzed human urine samples for asbestos fibers. Seven residents of an area where tap water contained $\sim 200 \times 10^{6}$ f/ℓ (chrysotile) donated early morning urine samples over a 21-month period. The donors resided in the area <3 years ($n=3$) or >20 years ($n=4$). Four control donors resided in an area where the fiber content of the tap water was 100 times less than that of the test community. The fiber content of the urine of the <3-year residents was significantly different ($p<0.05$) from the fiber content of the urine of the >20-year residents. This may be attributed to a high fiber content in the urine of one >20-year resident. The test group as a whole did not differ significantly from the controls with regard to urine fiber content. The authors recognize some problems associated with the study (e.g., fiber contamination of control water samples and, difficulties associated with the estimation of fibers in urine by use of present techniques). Yet, the numbers of fibers in the urines would have to increase at least 10-fold in order to obtain a convincing difference. Such a difference would probably not be accounted for by the problems of measurement. Thus, the authors state that even though the data are inconclusive, they suggest no relationship between high concentrations of fibers in drinking water and the numbers estimated for voided urine.

Summary

An important factor to consider when discussing the health risks associated with exposure to asbestos in drinking water is whether the fibers can penetrate the GI mucosa and thus reside in tissue. The weight of evidence is in favor of the occurrence of this event. However, the percentage of fibers shown to actually penetrate is small considering the total amounts ingested. Nevertheless, the penetration and tissue accumulation occurs, if only to a limited extent, and may be a factor in increased cancer risk from the ingestion of asbestos fibers.

Little is known about the metabolism of ingested fibers and there is no available information on the bioaccumulation/retention of ingested asbestos fibers. Simulated gastric juice has been demonstrated to alter the physical and chemical properties of chrysotile fibers and to a lesser extent, crocidolite fibers. One study on humans provides evidence that asbestos fibers pass through the GI mucosa and appear in the urine; another study on humans is inconclusive but suggests no relationship between the ingestion of fibers from drinking water and the elimination of fibers in urine.

IV. HUMAN EXPOSURE

Humans may be exposed to chemicals such as asbestos from a variety of sources, including drinking water, food, ambient air, occupational settings and consumer products. This analysis of human exposure to asbestos is limited to drinking water, food and ambient air because those media are considered to be sources common to all individuals. Even in limiting the analysis to these three sources, it must be recognized that individual exposure will vary widely based on many personal choices and on several factors over which there is little control. Where one lives, works and travels, what one eats, and physiologic characteristics related to age, sex and health status can all profoundly affect daily exposure and intake. Individuals living in the same neighborhood or even in the same household can experience vastly different exposure patterns.

In the Exposure Estimation Section of this chapter, available information is presented on the range of human exposure and intake for asbestos from drinking water, food and ambient air for the 70 kg adult male. It is not possible to provide an estimate of the number of individuals experiencing specific combined exposures from those three sources. However, the Summary Section of this chapter provides some insight into the relative contributions of the three sources, especially drinking water, to the range of intake values suggested by the available data.

Exposure Estimation

Drinking Water. According to U.S. EPA (1980) asbestos is commonly found in domestic water supplies. The two main asbestos-forming minerals analyzed for in the drinking water studies obtained are those referred to as chrysotile and amphibole fibers. The chrysotile fibers, a serpentine mineral, are a type of layered silicate (Zussman, 1978). They are also the most commonly found asbestiform fibers in drinking water (Millette et al., 1980). The amphibole fibers are a type of chain silicate (Zussman, 1978). Almost no information was found to indicate the typical sizes of each fiber type, although Millette et al. (1980) presented size characteristics of asbestos fibers found in certain state water supplies, which are presented in Table IV-I. Several studies on the occurrence of asbestos in drinking water are presented below. The studies report concentrations of asbestos fibers found by electron microscopy (EM).

Millette et al. (1979, 1980) compiled data on asbestos concentrations in over 1500 water samples from supplies in 406 cities in 47 states, the District of Columbia and Puerto Rico. In addition to finished and distribution water samples, the data base contained information on raw water and plant discharge effluents. Of the samples, 46% (from 186 of the cities) contained detectable amounts of asbestos. These were mainly chrysotile fibers, but amphibole fibers were also found. Of the samples, ~28% (from 113 cities) had values reported below one million fibers/liter (MFL), just >8% (from 33 cities) had values reported between 1-10 MFL, and ~10% (from 40 cities) had reported values >10 MFL. Another 25% of the samples (from 103 cities) had values considered not statistically significant (<0.5 MFL). The concentrations of chrysotile and amphibole fibers in the samples ranged from 0.01->9999.99 MFL and from 0.01-644 MFL, respectively. The high values for both types of fibers were from distribution water samples; the high value for the chrysotile fibers was from a supply in Louisiana and that for the amphibole fibers was from a supply in Minnesota.

TABLE IV-I

Some Size Characteristics of Asbestos Fibers Found in Various Water Supplies[a]

Source (State)	Type of Fiber	Number of Fibers Measured	Average Length (µm)	Average Width (µm)	Average Aspect Ratio[b]	Maximum Length Found (µm)
Reservoir with natural erosion (WA)	Chrysotile	289	0.8	0.034	25:1	3
Reservoir with natural erosion (CA)	Chrysotile	644	1.3	0.04	39:1	10
Cistern with asbestos tile roof (VI)	Chrysotile	342	2.3	0.04	62:1	25
Distribution sites from five asbestos cement pipe systems (SC, PA, FL)	Chrysotile	1440	4.3	0.044	121:1	80
Lake Superior (MN)	Amphibole	468	1.5	0.18	11:1	14

[a] Source: Millette et al., 1980

[b] Aspect ratio:Length/width

Millette et al. (1979) reported studies on asbestos contamination in water supplies near Lake Superior. Deposits of asbestos near this area are related to mining processing discharge. Before 1977, drinking water samples from Duluth, MN were found to contain amphibole fiber concentrations up to 644 MFL. However, since filtration treatment began in 1977, concentrations have decreased considerably. Recent data suggest that the fiber concentrations in Duluth drinking water are now <0.1 MFL and often <0.01 MFL.

Two Harbors, MN is another Lake Superior city sampled for asbestiform fibers (Millette et al., 1979). Before the filtration process was started in 1978, amphibole fiber concentrations as high as 200 MFL were reported. Millette et al. (1979) estimated that Two Harbor residents were probably exposed to levels as high or higher than Duluth residents because the mining discharge is closer to Two Harbors than Duluth.

Beaver Bay, MN is another city that Millette et al. (1979) estimated may receive values as high or higher than Duluth due to its closer proximity to mining discharge. Amphibole fibers were reported as high as 92 MFL for drinking water samples taken before 1979, the year that filtration was supposed to begin in Beaver Bay.

Several studies also reported findings for Pacific coast water supplies. Water supply samples from the Lake Crystal Reservoir in San Francisco contained concentrations of chrysotile fibers as high as 130 MFL. Erosion of the serpentine rock formation was reported as the primary cause of contamination in the Bay area. A total of 34 finished water samples were found to contain >1 MFL; 50% of those samples had concentrations of asbestos >10 MFL (Millette et al., 1979).

In a study of chrysotile asbestos fibers in California waters, Hayward (1984) analyzed groundwater samples from five wells and the reservoir that recharged them (located in the San Luis Obispo area). The wells were essentially recharged through serpentine rock. The reported range of values was from 2.6-170 MFL. The reservoir concentration was an order of magnitude higher than the highest well value.

Several samples from water supplies in Everett, WA were found to contain >100 MFL of chrysotile fibers (Millette et al., 1979). The presence of these fibers, as well as amphibole fibers found, was probably due to natural erosion into the reservoir water supply. Polissar et al. (1982) reported a range from 37-560 MFL for drinking water supplies in Everett, WA. Samples from the Tolt River water supply (serving Seattle, WA) were found to contain up to 25 MFL of chrysotile fibers (Millette et al., 1979).

Water supplies were sampled from several cities in New Mexico (Millette et al., 1979). Samples from supplies in Socorro, New Mexico contained up to 2190 MFL of chrysotile fibers, while samples from three other cities (Algodones, Pojoaque, and Santa Fe) were found to have levels in excess of 100 MFL. However, four sites in Socorro were apparently resampled using a more accepted technique and found to have a high value of 0.6 MFL. Whether the change in the reported values in Socorro is due to contamination in one of two wells taken out of service before the second sampling or due to method inaccuracies or contamination is unknown.

Cisterns, which collect drinking water from asbestos-tile type roofing material, have also been found to contain chrysotile fibers (Millette et al., 1979). Kentucky rainwater from a "life-time asbestos roof" contained 360 MFL of chrysotile fibers. Millette et al. (1980) reported levels of chrysotile fibers >500 MFL from drinking water samples from cisterns using asbestos tile roofing materials for collecting rainwater. However, other types of asbestos roofing do not contribute to drinking water contamination. Water samples from the more common asphalt asbestos shingles in Kentucky (30 years old) and Ohio (2 years old) were found to contain no asbestos. It was concluded in Millette et al. (1979) that asphalt binds fibers well enough to prevent significant number of fibers from entering the water supply.

Asbestos-cement (A/C) pipe may also contribute asbestos to municipal water supplies. Concentrations in A/C pipe distribution systems were found to be as high as 38 MFL of chrysotile fibers in one Florida city and 47 MFL in a Kentucky system (U.S. EPA, 1980). Samples at the end of a little-used A/C pipe system in Massachusetts contained as high as 480 MFL of chrysotile fibers (Millette, 1976). Samples from a Bishopville, SC distribution A/C pipe system contained >500 MFL of chrysotile fibers (Millette et al., 1979).

Distribution water samples from 45 Connecticut A/C pipe systems were shown to have concentrations of <1 MFL of asbestos (type unspecified), with the exception of one system that contained 10 MFL. However, the high value system was resampled twice and found to be <1 MFL in each case. It was concluded that the high count may be due to pipe tapping, i.e., adding a service connection to an existing pipe, which requires cutting a hole in the pipe (Millette et al., 1979). Pipe tapping was also felt to be the cause of a high value of 190 MFL from a sample at the dead end of an Amherst, MA system; no fibers had been found in distribution samples from this system (Millette et al., 1979).

A large number of effluent discharges from asbestos related industries have been analyzed for fibers (Stewart, 1976) with reported ranges of <1-1x10^6 MFL. However, it has not been shown that these enter the public water supply. Samples from city water supplies in Atlanta; Philadelphia; and Danville, KY that use rivers as the source of their water, contained asbestos (type unspecified) in excess of 10 MFL. The contamination in these three cities was thought to be due to erosion of asbestos waste piles into the river (Millette et al., 1979). Contaminated samples from a water supply in Kentucky, also due to erosion of old asbestos waste piles, contained as high as 74 MFL of chrysotile fibers (Millette et al., 1980).

Millette et al. (1979) concluded, based on very limited data, that the majority of water consumers in the largest U.S. cities are not exposed to concentrations of asbestos >1.0 MFL. The levels of asbestos observed in drinking water vary greatly in the studies obtained. Stewart (1976) reported a value as high as 1x10^6 MFL from effluent discharges. However, no evidence exists that these levels entered the public water supply. Another system in New Mexico (Millette et al., 1979) apparently contained a sample with a concentration of 2190 MFL. However, when the system was resampled using a more accepted technique, the high value was 0.6 MFL. Assuming that asbestos is present at the highest accurate concentration reported in a public water supply, i.e., >9999.99 MFL in Millette et al. (1979), the daily intake for the 70 kg adult male consuming 2 ℓ of drinking water/day would be >20 billion fibers/day.

Diet. Limited quantitative information is available on the contribution of food products to the total asbestos exposure of the U.S. population. Asbestos contamination of foods may occur directly due to the release of asbestos fibers into the food from filters used to purify the product (U.S. EPA, 1980) or indirectly due to the erosion of asbestiform minerals used in the building materials of the food industry (Huff, 1978).

Rowe (1983) indicated that dietary materials that have been reported to contain, or are likely to contain, asbestos include foods such as vegetable oil, lard, mayonnaise, ketchup and meats (Merliss, 1971; Wolff and Oehume, 1974; Albright et al., 1979); and beverages such as beers, sherries, ports, vermouth and soft drinks (Biles and Emerson, 1968; Cunningham and Pontefract, 1973; Wehman and Plantholt, 1974). Table IV-II summarizes the levels of asbestos in the beverages mentioned previously. It is not known whether the source of the asbestos in beverages could be the drinking water from which the drinks were made or the filtration process used by the food industry.

No information was available from the Food and Drug Administration (FDA) on the occurrence of asbestos in food.

TABLE IV-II

Concentration of Asbestos in Beverages

Dietary Substance	No. of Observations	Concentration, Million Fibers/ℓ[a]
Beer	4	1.1-6.6
Sherry	3	2-2.6
Port	1	2.1
Vermouth	2	1.8-11.7
Soft drinks	4	1.7-12.2

[a] Source: U.S. EPA, 1982, as cited in Rowe, 1983

[b] Analyzed by electron microscopy.

Rowe (1983) estimated that the daily intake of asbestos from a 12-ounce can of beer was 2.4×10^6 EM fibers; the daily intake from 3 ounces of talc-coated rice ranged from 7.8×10^9-3.1×10^{11} fibers.

Air. Limited information was obtained on the presence of asbestos in ambient air. Information on the typical size of airborne asbestos fibers is not well documented. Nicholson (1978) reported that asbestos fibers in ambient air tend to be very small; some fibers are up to 1 μm in length while most fibers are ~0.1 μm in length and have a diameter between 0.02-0.05 μm. More recently, however, Nicholson has stated that, based on monitoring practices in Germany, asbestos fibers from environmental exposures are more equivalent to those from occupational exposures (Rowe 1983).

The U.S. EPA reported a study of asbestos concentration in 187 quarterly composite samples from 48 U.S. cities collected from 1969-1970. The study showed that chrysotile asbestos was present in essentially all of the cities sampled (Nicholson, 1971; Nicholson and Pundsack, 1973). In the study, 98.5% of the samples contained concentrations of asbestos <20 ng/m^3, and 100% of the samples contained levels <100 ng/m^3. Nicholson (1971) reported a median value for this study of 1.6 ng/m^3. Of three samples that contained concentrations of asbestos >20 ng/m^3, one was from a city that had a major shipyard and another was from a city that had four brake manufacturers. Therefore, the samples could include a contribution from these specific sources in addition to the concentration in the ambient air (U.S. EPA, 1980).

U.S. EPA (1974) reported a median concentration of 2.3 ng/m³ for 127 samples from various U.S. cities. In that study, 98.5% of the samples contained levels of asbestos <20 ng/m³, while 100% of the samples contained levels <50 ng/m³ (U.S. EPA, 1974).

In a study of ambient air in New York City, Nicholson et al. (1971) collected samples in the five boroughs of New York (Manhattan, Brooklyn, Bronx, Queens, Staten Island). Samples were taken during daytime working hours and, due to construction and automobile activities, concentrations may have been higher compared to nighttime periods. Of the 22 samples taken in the five boroughs, a range of 2-65 ng/m³ was reported, with an overall average of 17.4 ng/m³. Nicholson et al. (1971) reported a median concentration of 13.7 ng/m³ for this study.

Nicholson et al. (1971) also conducted a study in lower Manhattan near sites where spraying of asbestos-containing fireproofing material was taking place. The study was to determine if such activity contributed to elevated asbestos levels. The results proved that the spraying did increase the air concentrations of asbestos as chrysotile fibers in 22 samples ranged from 3.5-375 ng/m³, with an overall average concentration of 40.9 ng/m³. Nicholson et al. (1971) reported a median concentration of 22.5 ng/m³ for this study.

Nicholson et al. (1975) reported variations in the average concentration of chrysotile asbestos fibers near 19 buildings at "outside air" sites (primarily office buildings) in five cities from 0-48 ng/m³. The number of samples, as well as the number of sites and their location were not reported.

Suta and Levine (1979) estimated that the rural U.S. population (~60 million people) was exposed to concentrations of asbestos from 0.01-0.1 ng/m^3. In contrast, they estimated that the urban U.S. population (~170 million people) were exposed to concentrations of asbestos >1 ng/m^3.

Thompson (1978) examined 20 samples obtained downwind from an emission source (location unknown) and found an average asbestos fiber concentrations ranging from 0.03-8200 ng/m^3. Thompson also investigated various industrial cities in the United States and found ranges of concentrations for the samples analyzed of 0.6-95.0 ng/m^3 in 1969-1970 (number of samples not given) and 0.4-27.7 ng/m^3 in 1971-1972.

Several airborne asbestos concentrations near industrial sites were reported in Rowe (1983). The ambient air concentrations near the Union Carbide mill and waste pile in King City, CA and near the Johns-Manville mill and water dump in Coalinga, CA were 1.03 million fibers/m^3 and 593 million fibers/m^3, respectively (U.S. EPA, 1982).

Summary

Table IV-III presents a general view of the total amount of asbestos potentially received by a 70 kg adult male from drinking water, food and air. Six separate exposure levels in drinking water, five exposure levels in air and one exposure level from food are shown in the table.

The data presented have been selected from an infinite number of possible combinations of concentrations for the three sources. Whether exposure occurs at any specific combination of levels is not known; nor is it

TABLE IV-III

Estimated Intake of Asbestos from the Environment by Adult Males in Millions of EM fibers/person/day

Concentration in Drinking Water (MFL)	Estimated Total Intake in Millions of EM Fibers/Person/Day (percent from drinking water) Based on Air Levels (ng/m^3) of:				
	Low		Moderate	High	
	0.01	0.1	2.0	20	8500
0.0	2.4 (0%)	2.6 (0%)	5.6 (0%)	34 (0%)	14,000 (0%)
0.1	2.6 (7.7%)	2.8 (7.1%)	5.8 (3.4%)	35 (0.6%)	14,000 (0.001%)
1.0	4.4 (45%)	4.6 (43%)	7.6 (26%)	36 (5.5%)	14,000 (0.01%)
10	22 (91%)	23 (87%)	26 (77%)	54 (37%)	14,000 (0.1%)
500	1,000 (100%)	1,000 (100%)	1,000 (100%)	1,000 (100%)	15,000 (6.7%)
10,000	20,000 (100%)	20,000 (100%)	20,000 (100%)	20,000 (100%)	34,000 (59%)

Intake from each source:

Water:
0.0 MFL: 0.0 million EM fibers/person/day
0.1 MFL: 0.2 million EM fibers/person/day
1.0 MFL: 2.0 million EM fibers/person/day
10 MFL: 20 million EM fibers/person/day
500 MFL: 1,000 million EM fibers/person/day
10,000 MFL: 20,000 million EM fibers/person/day

Food: 2.4 million EM fibers/person/day

Air:
0.01 ng/m^3: 0.0007 million EM fibers/m^3: 0.016 million EM fibers/person/day
0.1 ng/m^3: 0.007 million EM fibers/m^3: 0.16 million EM fibers/person/day
2.0 ng/m^3: 0.14 million EM fibers/m^3: 3.2 million EM fibers/person/day
20 ng/m^3: 1.4 million EM fibers/m^3: 32 million EM fibers/person/day
8,500 ng/m^3: 600 million EM fibers/m^3: 14,000 million EM fibers/person/day

possible to determine the number of persons that would be exposed to asbestos at any of the combined exposure levels. The data presented represent possible exposures based on the occurrence data and the estimated intakes. The drinking water levels selected are representative of the range of levels observed in the studies obtained. It is assumed that the 70 kg adult male consumes 2 ℓ of drinking water/day.

The dietary asbestos intake level selected was that reported by Rowe (1983) for the consumption of one beer/day. It was not expected that a significant portion of the U.S. population would consume talc-coated rice on a daily basis (see the Diet Section), since the use of talc-coated rice is limited mainly to certain ethnic groups.

Levels in ambient air were also chosen to be representative of the range of levels observed in the studies obtained. It was assumed that the 70 kg adult male inhales 23 m^3 of air/day (ICRP, 1975).

A factor of 70,000 EM fibers/ng of asbestos fibers was chosen for the conversion of data in ng/m^3 to EM fibers/m^3 (NRC, 1984). Numerous conversion factors have been reported, with variations of several orders of magnitude. For example, U.S. EPA (1980) reports factors between 5 and 150 μg/million light microscopy (LM) fibers (6.7-200 LM fibers/ng) and between 15 and 1000 EM fibers/LM fiber. Using these factors, a range of conversion factors between 100 and 200,000 EM fibers/ng of fibers would be suggested.

Conversion factors have generally been obtained in occupational settings; for this reason, they may not be appropriate for converting data to general ambient fiber concentrations since fiber sizes in the ambient environment appear to be smaller than those in occupational settings. The factor from NRC (1984) used in this exposure analysis was obtained by assuming that fibers in remote ambient environments far from asbestos sources would have average lengths of 1 μm and diameters of 0.1 μm, as compared to a mean length of 3 μm and a diameter of 0.3 μm assumed for occupational settings. Using these assumptions, NRC (1984) calculated values of 2000 EM fibers/ng for occupational settings vs. 70,000 EM fibers/ng for remote ambient environments. The latter value appears to be more representative of the fiber count/ng expected for the general U.S. population, and has been used here. The large potential error in this conversion factor should be noted, however. Due to the conversion error involved, Mike Beard, who is evaluating analytical techniques for asbestos at the U.S. EPA, advised against using any conversion factor.*

Assuming a moderate intake of 2.0 ng/m³ of asbestos fibers from air and a food intake of 2.4 million EM fibers/person/day, drinking water would be the predominant source of asbestos exposure in the adult male when drinking water levels exceed ~2.8 MFL. An accurate assessment of the number of individuals for which drinking water is the predominant source of exposure cannot be determined from the data since specific locations containing high concentrations of asbestos in drinking water and low concentrations of asbestos in ambient air and food are unknown.

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*Personal communication between Mike Beard, U.S. EPA, Research Triangle Park, NC, and Pauline Johnston, JRB Associates, McLean, VA.

The relative source contribution data are based on estimated intake and do not account for a possible differential absorption rate for asbestos by route of exposure. In addition, the effects of the chemical on the body may vary by different routes of exposure. The relative source contribution data also do not account for variations in asbestos fiber size. Exposures to total EM fibers have been reported without regard to size; however, the toxicological effects of asbestos appear to vary with fiber size (NRC 1984).

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V. HEALTH EFFECTS IN ANIMALS

The fate of asbestos in animals, as well as the specific physiological, biochemical, metabolic or morphologic effects caused by its presence are dependent on the organism involved, the route of administration, the length of exposure, the quality of exposure, synergistic or antagonistic interactions with other substances and the physical characteristics of the form of asbestos involved. In this chapter, the various types of health effects, both adverse and benign, associated with oral exposure to asbestiform fibers will be discussed.

Several recent studies have investigated the health effects of ingested asbestos fibers in animals. With the exception of one study, all work from 1977 to the present involves the detection of chronic health effects. The lack of acute effects studies appears not be be an omission but rather a consequence of the nature of health effects exerted by the exposure to asbestos (i.e., oncogenesis).

General Toxicity

Effects Associated with Acute Exposure. Effects resulting from the acute exposure of animals to asbestos are summarized in Table V-1.

Ingestion Studies -- Jacobs et al. (1978a) fed 3-month-old male MRC hooded rats 0.5 mg or 50 mg of chrysotile daily for 1 week and subsequently examined the GI tract tissue by light and electron microscopy. No effects were noted in esophagus, stomach or cecum tissue, but structural changes in the ileum, particularly of the villi, were seen. Clumps of nuclei and

TABLE V-1

General Toxicity of Asbestos

Species/ Test System	Sex	Route of Exposure	Dose	Duration	Health Effects	Reference
Acute Exposure						
Rat	M	ingestion	0.5 or 50 mg chrysotile/day	1 week	Practically no effects detected in the esophagus, stomach or caecum, but more discrete changes seen in the colon, rectum and small intestine.	Jacobs et al., 1978a
Human embryonic intestine-derived (I-407) cells	NR	in vitro	0.001-5.0 g/ℓ*	3 days	The amosite sample was the most cytotoxic. The drinking water samples were 100-fold less toxic than amosite. The order of toxicity of the drinking water samples was San Francisco > Seattle > Duluth.	Reiss et al., 1980b
Macrophages	NA	in vivo and in vitro	NR	-	Review article of the effects of asbestos on macrophages.	Miller, 1978
Malignant mouse macrophage-like cell line P388D	NA	in vitro	100 μg/mℓ of crushed quarried serpentine rock	72 hours	The fibrous serpentine (asbestos) was cytotoxic, while the platy serpentine (groundrock) had no effect on cell growth.	Frank et al., 1979
Human blood lymphocytes	NA	in vitro	400 μg/mℓ of chrysotile asbestos	72 hours	No cytotoxicity towards mononuclear cells was observed.	Kagamimori et al., 1980
Antibody-coated Chang cells	NA	in vitro	3 μg/mℓ or 5 μg/mℓ of chrysotile asbestos	20 hours	Antibody-dependent cell-mediated, cytotoxicity was inhibited by the presence of chrysotile.	
Subchronic Exposure						
Fischer 344 rats (6-week-old)	M	ingestion (intragastric administration)	10 mg, 3 times/week	10 weeks	No toxic effects were reported.	Ward et al., 1980
Chronic Exposure						
Rat	M	ingestion	0.5 or 50 mg chrysotile/day	14 months	Greatest changes in the mucosal lining cells of the ileum. Practically no effects detected in the esophagus, stomach or caecum, but more discrete changes seen in the colon, rectum and small intestine.	Jacobs et al., 1978a

*Samples contained serpentine and amphibole minerals
NR = Not Reported; NA = Not Applicable

mucinous material were present in the colon and rectum, though no morphological cellular changes were observed. The authors concluded that the observed changes were consistent with a mineral-induced cytotoxicity. In a subsequent report, Jacobs et al (1978b) found a significant increase in $[^3H]$-thymidine incorporation into DNA in the small intestinal mucosa, colon, rectum, spleen and stomach of rats following ingestion of 50 mg/day of chrysotile for 1 week. These results suggest that asbestos interferes with DNA metabolism in rat tissue. Finally, Jacobs and Richards (1980) demonstrated that asbestos may interfere with the active transport of glucose across the small intestine wall of a rat following 10 weeks of ingesting 50 mg chrysotile/day. The mean level of radiolabeled glucose was significantly lower in the chrysotile fed rats than in the controls.

A single oral dose of 5-100 mg chrysotile/kg to rats (3-8/dose) produced a subsequent increase in $[^3H]$-thymidine in the stomach (5 and 25 mg chrysotile/kg), duodenum (25 and 50 mg chrysotile/kg) and jejunum (5, 25, 50 and 100 mg chrysotile/kg) after 3 days (Amacher et al., 1975). The authors suggested that cellular proliferation and DNA synthesis may, therefore, be stimulated by chrysotile ingestion. In a study of asbestos carcinogenicity, Donham et al. (1980) noted a significant reduction in cyclic-AMP levels in the colons of asbestos-fed animals compared with controls (see Other Effects, Carcinogenicity Section).

In Vivo and In Vitro Studies -- The effects of chrysotile asbestos on mononuclear cells in vitro were studied by Kagamimori et al. (1980). Human blood lymphocytes were cultured with 400 μg chrysotile/mℓ and observed after 24, 48 and 72 hours of incubation. Chrysotile asbestos was found not to be cytotoxic to these cells. In an antibody-dependent cell-mediated cytotoxicity experiment, the same investigators demonstrated that antibody-coated Chang cells and effector cells cultured with chrysotile (3 and 5 μg/mℓ) showed a significant decrease in the release of ^{51}Cr as compared with controls. The inhibition of the antibody-dependent cell-mediated cytotoxicity by chrysotile asbestos appeared to be due to the prevention of contact between antibody-coated target cells and effector cells.

Reiss et al. (1980b) assessed the toxicity of six asbestos-containing particulate samples of drinking water from locations throughout the United States. Human embryonic intestine epithelial cells (1-407) were used for the cytotoxicity assay. The assay was quantified by measuring the inhibition of the 1-407 cell colony formation following exposure to 0.001-5 g/ℓ of each particulate sample. San Francisco drinking water samples containing 7.2% chrysotile inhibited colony formation by 96% at a dose of 1 g/ℓ. A Seattle drinking water concentration of 2.5 g/ℓ was found to inhibit 73% of colony formation. This sample was known to contain 2% chrysotile. The drinking water sample from Duluth, which contained amphibole crystals, was found to be the least toxic of the drinking water samples with 88% cell colony inhibition occuring at a concentration of 5 g/ℓ. Concentrations below those mentioned inhibited less than 50% of the cell colonies. The authors concluded that asbestos exerted its cytotoxicity through a specific physiochemical mechanism. They did not provide details of the specific nature of this mechanism.

Effects Associated with Subchronic Exposure. Ward et al. (1980) fed 6-week-old male F344 rats 10 mg of asbestos 3 times/week for 10 weeks. The animal tissues were examined at 34 weeks or after their natural death. Intestinal cancer (not significant) was observed; however, no toxic effects were reported.

Effects Associated with Chronic Exposure. There are few noncarcinogenic effects associated with the chronic ingestion of asbestos. In addition to the acute study performed by Jacobs et al. (1978a) and described earlier, Jacobs et al. (1978a) also fed 3 month-old male MRC hooded rats 0.5 mg or 50 mg chrysotile daily for 14 months. Rats fed 50 mg/day for 14 months had the greatest changes in the mucosal lining cells of the ileum; otherwise, the results were similar to those of the acute exposure studies (i.e., marked tissue changes in the ileum, clumps of nuclei and mucinous material present in the colon and rectum though no morphological changes, and practically no effects in the esophagus, stomach and caecum).

Detailed pathology was conducted in the studies of the effects of ingesting amosite and chrysotile in hamsters and amosite in F344 rats by the National Toxicology Program (NTP, 1982a,b,c). No nonmalignant effects were noted at a greater frequency than in control animals in any study. The details of these studies are discussed in the section on Carcinogenicity.

Target Organ Toxicity

No specific organ has been identified as a target organ following the ingestion of asbestos fibers. Changes were detected in the colon, rectum and small intestine and, to a greater extent, in the mucosal lining cells of the ileum following longer exposure durations. Cytotoxic effects have been demonstrated through in vitro testing procedures.

Other Effects

Carcinogenicity.

Oral Administration -- Condie (1983) recently reviewed the animal studies on ingested asbestos other than the large-scale feeding studies conducted by the NTP of the National Institute of Environmental Health Sciences (NIEHS). Table V-2, adapted from Condie (1983) summarizes the results of 12 oral studies. Smith (1973) reported results of feeding 45 hamsters 1% chrysotile or amosite in their diet. One neoplasm with no detectable asbestos was observed in the mesentary of the colon. However, the finding of fibers in tumor tissue would be unlikely and, as these tumors are rare in hamsters, this result cannot be totally dismissed. No relevant experimental details, including the dosage of asbestos, was provided. Webster (1974) reported that baboons (number not reported) exposed to "heavy" concentrations (amount not reported) of asbestos in food and drinking water for 5 years did not develop any peritoneal or GI tumors. The 5-year observation time in this species is too short for any meaningful conclusions to be drawn from this experiment.

Gross et al. (1974) reported the result of a series of feeding experiments using rats fed chrysotile and crocidolite in concentrations of 5-10 mg/day for 21 months. The data were the unpublished results of various experiments conducted over the previous 10 years by three different laboratories. No evidence of cancer or any other type of lesion was found from

TABLE V-2

Summary of Asbestos Ingestion Carcinogenicity Studies[a]

Species	Test Material	Dose	Exposure Time	Study Duration	No. Animals	Malignant Tumors		Reference
					Initial/Examined	No.	Location Type[b]	
Rat	crocidolite	0.15% in diet ad lib	78 wk	78 wk	40/12	0		Bonser and Clayson, 1967
	control	0	0	86 wk	65/25	1	Liver-S	
Rat	chrysotile	5% in diet ad lib	21 mo	21 mo	10/10	0		Gross et al., 1974
	control	0	0	21 mo	5/5	0		
Rat	chrysotile	10 mg/wk	16 wk	1.5 yr	31/31	2	Breast-C	Gross et al., 1974
	crocidolite	5 mg/wk	16 wk	1.5 yr	33/33	0		
	crocidolite	10 mg/wk	16 wk	1.5 yr	34/34	1	Node-L	
	control	0	0	1.5 yr	24/24	5	3 Breast-C, Thigh-S, Node-L	
Rat	crocidolite (2 sources)	10 mg/wk	18 wk	1.5 yr	63/63	0		Gross et al., 1974
	control	0	0	1.5 yr	24/24	0		
Rat	chrysotile	20 mg/day	life	441 days[c]	50/42	12	Lung-C, 4 Kidney-C, 3 Node-L, 4 Liver-C	Gibel et al., 1976
	talc	20 mg/day	life	649 days[c]	50/45	3	Liver-C	
	control	0	0	702 days[c]	50/49	2	Liver-C	
Rat	chrysotile	1% in diet ad lib	24 mo	24 mo	10/7	6	Brain-S, Pituitary-C, Node-L, 2 Kidney-C Peritoneum-S	Cunningham et al., 1977
	control	0	0	24 mo	10/8	1	Peritoneum-S	
Rat	chrysotile	1% in diet ad lib	24 mo	30 mo	40/36	11	2 Thyroid-C, Thyroid-S, Liver-C, Chemodectoma jugular body, Colon-C, Ileum-S, Adrenal-C, 2 Node-L, Bone-S	Cunningham et al., 1977
	control	0	0	30 mo	40/32	11	Thyroid-C, Liver-C, 2 Adrenal-C, Kidney-C, Node-L, 5 Fat-S	

TABLE V-2 (cont.)

Species	Test Material	Dose	Exposure Time	Study Duration	No. Animals	Malignant Tumors		Reference
					Initial/Examined	No.	Location Type[b]	
Hamster	amosite	0.5 mg/ℓ ad lib	23 mo	23 mo	60/60	1	Lung-C	Smith et al., 1980
	amosite	5 mg/ℓ ad lib	23 mo	23 mo	60/60	3	2 Stomach-C, Peritoneal Mesothelioma	
	amosite	50 mg/ℓ ad lib	23 mo	23 mo	60/60	0		
	taconite tailings	0.5 mg/ℓ ad lib	23 mo	23 mo	60/60	1	Uterus-S	
	taconite tailings	5 mg/ℓ ad lib	23 mo	23 mo	60/60	0		
	taconite tailings	50 mg/ℓ ad lib	23 mo	23 mo	60/60	0		
	control	0	0	23 mo	120/120	1	Node-L	
Rat	chrysotile	10% in diet ad lib	32 mo	32 mo	240/189	4	3 Colon-C, Abdominal Mesothelioma	Donham et al., 1980
	cellulose fiber	10% in diet ad lib	32 mo	32 mo	242/197	2	Colon-C	
	control	0	0	32 mo	121/115	3	Colon-C	
Rat	azoxymethane[d]	7.4 mg/kg wk	10 wk	34 wk	21/21	12	5 Ileum-C, 7 Colon-C	Ward et al., 1980
	azoxymethane plus amosite	7.4 mg/kg wk 10 mg, 3/wk	10 wk	34 wk	21/18	10	3 Ileum-C, 7 Colon-C	
	azoxymethane plus chrysotile	7.4 mg/kg wk 10 mg 3/wk	10 wk	34 wk	21/21	10	4 Ileum-C, 6 Colon-C	
	amosite	10 mg 3/wk	10 wk	34 wk	21/21	0		
	chrysotile	10 mg 3 wk	10 wk	34 wk	21/21	0		
	saline	1.0 ml 3/wk (gavage)	10 wk	34 wk	21/21	0		
	untreated	-	0	34 wk	21/21	0		
	azoxymethane	7.4 mg/kg wk	10 wk	95 wk	50/48	39	12 Ileum-C, 27 Colon-C	
	azoxymethane plus amosite	7.4 mg/kg wk 10 mg 3/wk	10 wk	95 wk	50/48	44	15 Ileum-C, 29 Colon-C	
	saline plus amosite	1/wk (SC) 10 mg 3/wk	10 wk	95 wk	50/49	17	Ileum-C 16 Colon-C	

TABLE V-2 (cont.)

Species	Test Material[d]	Dose	Exposure Time	Study Duration	No. Animals	Malignant Tumors		Reference
					Initial/Examined	No.	Location Type[b]	
Rat	filtered Duluth tap water	1 mfℓ[e] ad lib	690 days[c]	690 days[c]	28/27	3	Lung-C, Ovary-C Forestomach-C	Wilding et al., 1981
	unfiltered Duluth tap water	100 mfℓ ad lib	960 days[c]	960 days[c]	30/28	4	Salivary Gland-C, Skin-C, Uterus-S, Mediastinum-L	
	Lake Superior water sediment	5000 mfℓ ad lib	840 days[c]	840 days[c]	22/22	3	Lung-C, Skin-C Uterus-S	
	taconite tailings	100,000 mfℓ ad lib	870 days[c]	870 days[c]	30/30	3	Neck-S, Chest Wall-S, Mediastinum-L	
	chrysotile/amosite	20 mg/day	870 days[c]	870 days[c]	30/30	7	Breast-C, 2 Fibrous Histiocytoma, Skin-C Mediastinum-L, Pleural Mesothelioma	
	amosite	300 mg/day	750 days[c]	750 days[c]	20/20	1	Leukemia	
	diatomaceous earth	20 mg/day	840 days[c]	840 days[c]	30/30	5	Salivary Gland-C, Uterus-S, Skin-C, Peritoneal Mesothelioma	
Rat	amosite	250 mg/wk	25 mo	life	24/24	1	Stomach-S	Bolton et al., 1982
	crocidolite	250 mg/wk	25 mo	life	22/22	1	Adrenal-C	
	chrysotile	250 mg/wk	25 mo	life	22/22	5	Fat-S, Pleural Histiocytoma, Adrenal-C, Plasma Cell Tumor	
	margarine control	0	0	life	24/24	4	Adrenal-C, Bladder-C, Peritoneum-S	
	control	0	0	life	23/23	2	Fat-S, Lymphoma	

[a] Source: Adapted from Condie, 1983

[b] C = carcinoma; S = sarcoma; L = lymphoma

[c] Mean survival time

[d] Azoxymethane and saline given subcutaneously, amosite, chrysotile and saline administered by oral gavage

[e] mfℓ = million amphibole fibers/liter

feeding "high" asbestos by gavage in butter or margarine for up to 21 months. No evidence of asbestos penetration in the GI mucosa was found. The experiments were flawed because of small numbers (24-30) in each group, limited administered doses and, most importantly, systematic histological examination was done on only 53 of over 200 animals. Further information on experimental procedures was not provided.

In rats fed 20 mg asbestos/day throughout their lifetime, 12/42 malignant tumors developed in the animals examined after 441 days (Gibel et al., 1976). Four of the malignancies were kidney carcinomas and three were lymphomas; no such tumors were found in the control group nor the group exposed to talc. While the filtering material was stated to contain 53% chrysotile asbestos, sulphated cellulose and a condensation resin, the absence of specific details on the other materials present is a serious deficiency.

Cunningham et al. (1977) conducted two lifetime feeding studies on a limited number of male Wistar rats. One percent chrysotile asbestos with 5% corn oil was added to a rat chow diet and fed to groups of 10 and 40 rats in two separate experiments. In the first study, 6 of 7 surviving animals were found with tumors, whereas one malignancy was observed in eight controls. No GI cancers were observed but two malignancies in the asbestos-fed animals were kidney nephroblastomas. In the second study, malignancies were observed in 11/40 asbestos-fed animals and 11/40 control animals. Two of the malignancies in the asbestos-fed group were in the GI tract; one of the malignancies in the control group was a nephroblastoma, which lessens the significance of these tumors in the asbestos group. The authors concluded that small amounts of asbestos can penetrate the lining of the GI tract but no conclusions could be drawn as to the carcinogenic potential of ingested asbestos.

Smith et al. (1980) studied six groups of 60 two-month-old hamsters exposed to 0.5, 5 or 50 mg/ℓ of amosite and taconite tailings in drinking water. Filtered water from Lake Superior was given to 120 control animals. In the low and intermediate amosite exposure groups, 4 malignancies [1 lung carcinoma, 2 stomach squamous cell carcinomas (noninvasive), 1 peritoneal mesothelioma] were found. However, no malignancies were identified in the highest exposure group and the authors did not attribute the observed malignancies to the asbestos exposure because of the absence of a consistent dose-response gradient.

Donham et al. (1980) initiated a lifetime study of male and female F344 rats fed 10% chrysotile in their diet. Similar numbers of colon cancers were observed in the exposed group (4/189), a group fed 10% cellulose fibers (2/197) and an undosed control group (3/115). The differences in the number of colon tumors were not significant. Actuarial analysis indicated that the asbestos-fed rats were at a greater risk for developing lesions (17.9%) than the cellulose-fed rats (13.6%) and control animals (8.2%). These differences are not statistically significant when comparing the asbestos-fed group with the other two groups. Although the development of colon tumors was not statistically different at the $p<0.05$ level, the authors concluded that the ingested asbestos may have had some role in colon carcinogenesis as evidenced by electron micrographs showing penetration by asbestos fibers in the lining of the GI tract, lowered cAMP levels and an increased cumulative risk in asbestos-fed animals to develop colon lesions.

Ward et al. (1980) also investigated the cancer-promoting potential of ingested asbestos. Groups of 21 rats were exposed to azoxymethane plus amosite or chrysotile for 10 weeks. Single agent and untreated controls were also studied. Observations on malignancies were made after 34 and 95 weeks of exposure. Cancers of the ileum and colon were found in all azoxymethane-exposed groups, but no statistically significant increase in numbers was detected in those animals exposed to amosite or chrysotile plus azoxymethane. One amosite-exposed group showed a high frequency of colon cancer, but the possibility of an inadvertent exposure to azoxymethane must be considered since seven rats in the amosite group developed Zymbal gland tumors (which can be induced by azoxymethane). This study did not demonstrate a cocarcinogenic effect of amosite or chrysotile. It was also limited by the short administration period of the asbestos. If the asbestos acts as a promoter, it would have been desirable to have continued administration to assure the presence of fibers at potential sites of cancer over the lifetime of the animals.

Two small studies have recently been reported. One by Hilding et al. (1981) was designed to investigate the potential carcinogenic effect of taconite tailings, amosite and diatomaceous earth in drinking water. Groups of 20-30 rats were supplied water with these various materials throughout their lifetime. A variety of malignancies were found in each exposure group, although none were attributable to asbestos exposure. However, a pleural mesothelioma was identified in a group exposed to amosite plus chrysotile and a peritoneal mesothelioma was identified in the diatomaceous earth exposed group. A study by Bolton et al. (1982) examined the carcinogenic effects of asbestos on groups of 22-24 animals fed 250 mg/week of amosite, crocidolite or chrysotile in margarine for up to 25 months. No excess malignancies were found in the exposed group compared with the margarine or undosed control groups.

Four studies on the chronic effects of dietary exposure to fibers have been published by the NTP (1982a,b,c, 1984) and presented by McConnell et al. (1983a,b). Two of these studies investigated the effects of dietary exposure to amosite and chrysotile asbestos in Syrian golden hamsters. Groups of ~240 male and female hamsters were fed 1% by weight of either amosite or 1 of 2 samples of chrysotile asbestos [one short range (SR) and the other intermediate range (IR) in length] in test diets. Male and female groups of ~175 animals were fed IR chrysotile and oral doses of 4 mg/kg 1,2-dimethylhydrazine dihydrochloride (DMH) every other week for 10 weeks. For each exposure group four male and four female control groups of ~125 animals each were studied. Male and female control groups of ~125 animals each were exposed to DMH alone. The only group to show a significant ($p<0.05$) increase in overall primary tumors was the chrysotile group. This increase was due primarily to adrenal cortex tumors. Male hamsters receiving SR chrysotile or the combined DMH/IR chrysotile exposure also showed an overall primary tumor increase relative to pooled controls. However, when survival differences were taken into account, the excesses were not statistically significant. Significant increases in cortical adenomas were seen in male and female IR chrysotile-exposed groups when compared with pooled controls, but not when compared with temporal controls. None of the treated groups showed an increased risk of malignancy in the GI tract. The absence of GI tumors was believed to weaken any association of adrenal tumors with chrysotile exposure. None of the male or female animals that were administered DMH, with or without chrysotile asbestos, showed significant increases in intestinal cancer. Thus, under the conditions of the bioassay, amosite asbestos SR or IR chrysotile asbestos were not shown to be carcinogenic when ingested by male and female Syrian golden hamsters. The carcinogenic studies of the combined exposure to IR chrysotile asbestos and DMH are considered inadequate because of no increase in intestinal neoplasia in the DMH group.

Experiments similar to the hamster studies have been conducted by McConnell et al. (1983b) to determine the chronic effects of ingestion of amosite asbestos and nonfibrous tremolite in F344 rats. One percent tremolite or amosite asbestos by weight was incorporated into the animals diet and fed to groups (n=100-250) of male and female rats for their lifetime (this includes prenatal exposure as a result of dams being fed asbestos during gestation). Male and female animals, in groups of 175 each, were exposed to amosite and 5-15 mg/kg DMH. Positive controls of 125 male and 125 female animals were exposed to DMH alone. Male and female groups of 100 rats were given 470 mg/kg bw chrysotile by gavage before weaning (21 days post partum) and subsequently fed the amosite diet. A significantly increased incidence of C-cell carcinoma of the thyroid was found in amosite-treated male rats. Nonsignificant increases were seen in female rats and both the male and female groups that underwent preweaning gavage. No excess neoplasms of the GI tract were found in any treated group, nor were any excess carcinomas found at any site in the tremolite-exposed rats. A very high incidence of GI neoplasia was experienced by the DMH and the DMH-amosite groups. However, the overall incidences of cancer at different sites were similar in the DMH and DMH-amosite groups, but some specific differences occurred. For example, 11% of the DMH-amosite group developed cancer of the duodenum versus 2% of the controls. On the other hand, 9% of the DMH controls developed neoplasms of the jejunum versus 1% in the DMH-amosite group. Overall, the data suggest that amosite asbestos has neither a cocarcinogenic nor protective effect on the carcinogenic potential of DMH. However, the very high incidence of cancer in the DMH-exposed groups precluded a definitive statement on the role of asbestos as a cocarcinogen or promoter. Under the conditions of the lifetime bioassay, neither tremolite nor amosite asbestos was found to be carcinogenic when ingested at the level of 1% diet in male and female F344 rats.

In a more recent study, groups of 88-250 male and female F344 rats were exposed to 1% chrysotile asbestos (SR and IR fibers) in their diet as part of a lifetime carcinogenicity study (NTP, 1984). Exposure began with the dams of the test animals. A subgroup of 100 male and female chrysotile exposed rats received 0.47 mg/g of the IR fibers in drinking water by gavage during lactation. At 9 weeks of age, another subgroup of 125-175 control and asbestos-exposed rats were given 1,2-dimethylhydrazine dihydrochloride (7.5 mg/kg for males, 15 mg/kg for females) by gavage every other week for 10 weeks (5 doses). No signs of maternal or fetal toxicity were observed in the asbestos exposure group. Males and females exposed over their lifetime also showed no overt signs of toxicity. Benign epithelial neoplasms (adenomatous polyps), however, were found in the large intestine of some male rats (9/250, p=0.08) fed the IR asbestos. The incidence of these neoplasms was highly significant (p=0.003) when compared with the incidence of epithelial neoplasms (benign and malignant) in male controls (3/524). Therefore, NTP (1984) claimed there was "some" evidence of carcinogenicity in male rats exposed to IR chrysotile fibers. No evidence for carcinogenicity was found in male and female rats exposed to the SR fibers. The coadministration of 1,2-dimethylhydrazine dihydrochloride and IR asbestos "did not indicate that IR chrysotile asbestos had either a tumor-enhancing or protective effect" (see Chapter VIII).

In summary, with the exception of the NTP (1982a,b,c, 1984) animal experiments, few of the earlier studies allowed a definitive conclusion to be drawn with respect to the carcinogenicity of ingested asbestos. Most studies involved very few animals and an occasional suggestive tumor, such as mesothelioma, could not be unequivocably associated with the asbestos exposure. Conversely, positive studies such as that of Gibel et al. (1976) were marred because of the absence of information on possible exposures to other carcinogenic materials. The NTP (1982a,b,c) studies on the ingestion of amosite and chrysotile asbestos by hamsters and amosite asbestos by F344 rats at the 1% level did not indicate any carcinogenic effect of ingested asbestos. In the NTP (1984) male rats ingesting IR chrysotile fibers at 1% in the diet had a significant increase in benign epithelial neoplasms in the large intestine. This is interpreted as limited evidence that ingested chrysotile asbestos fibers may be carcinogenic. Further research is needed to clarify this issue.

Intraperitoneal Administration -- Intraperitoneal injections of 20 mg crocidolite or chrysotile produced three peritoneal mesotheliomas in 13 CD rats. No tumors were produced by 20 mg of amosite in a group of 11 rats (Maltoni and Annoscia, 1974). The same investigators also injected 25 mg crocidolite into 50 male and 50 female 11-week-old Sprague-Dawley rats and observed 31 mesothelial tumors in males and 34 in females.

In an extensive series of experiments, Pott and Friedrichs (1972) and Pott et al. (1976) produced peritoneal mesotheliomas in mice and rats injected with various commercial varieties of asbestos and other fibrous material. These results are shown in Table V-3. With use of ball-milled in comparison to native fibers, the rate of tumor production was reduced from 55% to 32% and the time from onset of exposure to first tumor was lengthened from 323 days to 400 days following administration of four doses of 25 mg UICC Rhodesian chrysotile. In the case of the ball-milled fiber, 99% were reported to be <3 μm, 93% <1 μm and 60% <0.3 μm. The data suggest that large-diameter fibers (>3 μm) are more carcinogenic than finer fibers. The origin of the reduced carcinogenicity of shorter, ball-milled fibers is less clear as the relative contributions of shorter fiber length and the significant alteration of the crystal structure by input of physical energy are not, as yet, defined. Furthermore, the extrapolation of data developed on size-dependent effects, from intrapleural or i.p. administration to inhalation (where movement of the fibers in airways and subsequently through body tissues is strongly size-dependent) presents significant difficulties. Finally, since the number of smaller fibers in an exposure circumstance may be 100 times greater than those >5 μm in length, the reduction of their carcinogenicity must be demonstrated at a level 100 times less before their contribution can be neglected.

Mutagenicity. In a preliminary study, chromosomal aberrations were seen in Chinese hamster cells cultured in a medium containing 0.01 mg/mℓ of either chrysotile or crocidolite (Sincock and Seabright, 1975). No chromosomal aberrations were seen in culture with coarse glass fibers or

TABLE V-3

Tumors in Abdomen and/or Thorax after Intraperitoneal Injection of Glass Fibers, Crocidolite or Corundum in Rats[a]

Dust	Form[b]	Dose (i.p.)	Effective No. of Dissected Rats	No. of Days Before First Tumor	Average Survival Time of Rats with Tumors (days after injection)	Rats with Tumors (%)	Tumor Type[c]					
							1	2	3	4	5	6
Glass fibers MN 104	f	2	73	421	703	27.4	17	3	-	-	1	1
Glass fibers MN 104	f	10	77	210	632	53.2	36	4	-	1	3	-
Glass fibers MN 104	f	2x25	77	194	367	71.4	47	6	2	-	-	-
Crocidolite	f	2	39	452	761	38.5	12	3	-	-	2	1
Corundum	g	2x25	37	545	799	8.1	1	-	-	2	2	2
UICC Rhodesian chrysotile	f	2	37	431	651	16.2	4	2	-	-	1	-
UICC Rhodesian chrysotile	f	6.25	35	343	501	77.1	24	3	-	-	-	-
UICC Rhodesian chrysotile	f	25	31	276	419	80.6	21	2	1	1	-	-
UICC Rhodesian chrysotile	f	4x25	33	323	361	54.5	16	2	-	-	-	-
UICC Rhodesian chrysotile	f	3x25 s.c.	33	449	449	3.0	-	-	1	-	-	-
UICC Rhodesian milled	f	4x25	37	400	509	32.4	9	3	-	-	-	-
Palygorscite	f	3x25	34	257	348	76.5	24	2	-	-	-	-
Glass fibers s + s 106	f	2	34	692	692	2.9	1	-	-	-	-	-
Glass fibers S + S 106	f	10	36	350	530	11.1	2	2	-	-	1	-
Glass fibers S + S 106	f	4x25	32	197	325	71.9	20	3	-	-	-	-

TABLE V-3 (cont.)

Dust	Form[b]	Dose (i.p.)	Effective No. of Dissected Rats	No. of Days Before First Tumor	Average Survival Time of Rats with Tumors (days after injection)	Rats with Tumors (%)	Tumor Type[c]					
							1	2	3	4	5	6
Gypsum	f	4x25	35	579	583	5.7	-	-	1	1	1	-
Nemalite	f	4x25	34	249	315	73.5	17	8	-	-	-	-
Actinolite	g	4x25	39	-	-	-	-	-	-	-	-	-
Biotite	g	4x25	37	-	-	-	-	-	-	-	-	-
Haematite (precipit.)	g	4x25	34	-	-	-	-	-	-	-	-	-
Haematite (mineral)	g	4x25	38	-	-	-	-	-	-	-	-	-
Pectolite	g	4x25	40	569	569	2.5	-	-	-	1	1	1
Sanidine	g	4x25	39	579	579	2.6	-	1	-	-	-	-
Talc	g	4x25	36	587	587	2.8	1	-	-	-	-	-
NaCl (control)	-	4x2ml	72	-	-	-	-	-	-	-	-	-

[a] Source: Adapted from Pott and Friedrichs, 1972; Pott et al., 1976

[b] f = fibrous; g = granular

[c] Tumor types are: 1 = mesothelioma; 2 = spindle cell sarcoma; 3 = polymorphous sarcoma; 4 = carcinoma; 5 = reticulum cell sarcoma; 6 = benign - not evaluated in tumor rates

with control media. A more extensive series of experiments by Sincock (1977), using several chrysotile and crocidolite samples, showed that both positive transformation of morphology and positive genetic responses result from the passive inclusion of asbestos in culture media of CHO-K1 Chinese hamster cells. Very fine fibrous glass produced the same abnormalities seen in untreated cultured cells. The principal results are shown in Table V-4.

Chamberlain and Tarmy (1977) tested UICC asbestos samples of chrysotile, amosite, anthophyllite and samples of superfine chrysotile on several strains of *Escherichia coli* and *Salmonella typhimurium* bacterial systems in which mutagenicity to exogenous materials appears to correlate well with animal carcinogenic test data. *E. coli* tester strains included the following: B/r, WP2, WP2 uvrA and WP2 uvrA polA. Testing of asbestos for mutagenicity in *S. typhimurium* was limited to investigation of tester strains TA1535 and TA1538. No more recent studies were available providing data on testing of asbestos in the more sensitive strains TA98 and TA100. Doses ranged from 1-5000 μg/ℓ of asbestos for 72 hours. Several positive and negative controls were used in all experiments. No mutagenic activity was associated with asbestos over the wide range of concentrations for either test system. The authors pointed out that prokaryotic cells (bacteria) do not phagocytize the fibers as do eukaryotic cells, such as macrophages.

Asbestos appeared to have no independent mutagenic capability in testing of Syrian hamster embryo cells (Newman et al., 1980), but after 20 hours of interaction between chrysotile asbestos and the cultured cells, alterations were observed in glycolipids and glycoproteins located in the cell membrane surface. Since these changes were observed after prolonged exposure of the

TABLE V-4

Effects of Different Treatments on Chromosomes of CHO-K1 Chinese Hamster Cells*

Effect	SFA Chrysotile	Rhodesian Chrysotile a	Canadian Chrysotile b	UICC Crocidolite	UICC Anthophyllite	UICC Amosite	Glass 110	Control
Polyploids	28	23	27	26	2	14	3	4
Cells with fragments	13	14	11	10	10	16	0	0
Other abnormalities	33	9	15	29	9	13	0	0
Percent abnormal karyotypes	62	34	39	56	26	41	3	4

Effect	Rhodesian Chrysotile a	Rhodesian Chrysotile a Leached	Canadian Chrysotile b	Canadian Chrysotile b Leached	UICC Crocidolite	UICC Crocidolite Milled	Glass 110	Control
Polyploids	23	6	26	10	26	6	6	4
Cells with fragments	13	0	9	0	14	9	0	0
Other abnormalities	10	0	16	4	28	3	0	0
Percent abnormal cells	34	6	42	14	57	16	6	4

*This table summarizes the principal results reported in Sincock, 1977. Results were obtained using 48-hour exposure; 100 cells were scored from each culture. Categories of genetic damage were not mutually exclusive.

cells to asbestos, the data support the concept that a metabolic rather than a masking effect is involved. The authors theorize that the membrane changes incurred by asbestos serve to allow other mutagens to pass into the cell so as to act on the nuclear structure; however, this theory has not been experimentally pursued.

Teratogenicity/Reproductive Effects. Schneider and Maurer (1977) gave pregnant CD-1 mice (10-12/dose) 4, 40 or 400 mg asbestos/kg bw (1.43, 14.3 or 143 mg asbestos/mℓ) in their drinking water during days 1-15 of gestation. Water consumption did not vary between the different dosage groups. There was also no difference in embryo survival between the treatment groups and the controls, which received only tap water. There were no signs of maternal toxicity.

In a second study, Schneider and Maurer (1977) cultured 4-day-old mouse blastocysts in 1, 10 or 100 μg asbestos for 4 hours. The blastocysts were then transferred to day 3 or day 4 pseudo-pregnant mice. There were no significant differences in the rate of implantation between the asbestos exposed blastocysts and the controls. There was, however, a difference in fetal viability. A significant dose dependent relationship was reported in the number of dead and resorbed fetuses in the day 3 ($p=0.05$) and day 4 ($p=0.06$) pseudo-pregnant mice. It should be noted that the authors' level of significance was established as $p<0.10$. No dose response relationships were observed in the postimplantation mortality in day 4 mice. The day 3 mice were stated to show a dose dependent increase in fetal mortality ($p<0.05$). Other signs of fetotoxicity (decreased fetal weight, stunted fetuses and malformations) were not significantly different between the controls and asbestos exposure groups. Electron micrographs indicated that the zona pellucida protected the trophoblast cells of the blastocyst from asbestos fibers.

The evidence supplied by Cunningham and Pontefract (1974) of transplacental transfer of asbestos supports the possibility of the occurrence of teratogenic or reproductive effects following asbestos exposure (see Chapter III the Absorption and Distribution:Injection of Asbestos Section).

Summary

General toxicity following the ingestion of asbestos is minimal with no specific target organ defined. The majority of experimental evidence indicates that the long-term, high-level ingestion exposure to various types of asbestos fibers failed to produce any definite, reproducible, organ-specific carcinogenic effect (Condie, 1983). The vast majority of the asbestos ingestion studies were either negative or equivocal. However, many of the studies suffered from serious limitations. Through studies performed, both limited in number and scope, asbestos has not been demonstrated to be either mutagenic or teratogenic. Data on the health effects of asbestos on animals are provided and summarized in Tables V-I and V-2.

VI. HEALTH EFFECTS IN HUMANS

Human health effects associated with the ingestion of asbestos have centered around malignancies. No known chronic nonmalignant effects have been associated with the ingestion of asbestos or other fibers in water. Effects in humans associated with acute exposures have been restricted to the identification of asbestos fibers in the urines of individuals ingesting the substances in water or other materials (Cook and Olson, 1979). The finding of fibers in body fluids has not been associated with any health effects. Auerbach et al. (1977) reported that the ingestion of contaminated Duluth water did not result in a great increase in the number of asbestos bodies present in lung tissue as viewed under a light microscope. Carter and Taylor (1980) examined liver, jejunum and lung tissue samples of persons with long-term (up to 15 years) high-level oral exposure to ferromagnesium silicate in Duluth, MN. This fiber type was found in significant numbers (60%) in the study group. The differences in concentration between tissues studied was not statistically significant. Greatest amounts were found in the lung followed by the liver and jejunum.

Of importance in the discussion of the effects of ingested asbestos fibers is an understanding of the effects of inhaled asbestos fibers. This latter exposure results not only in lung cancers but in cancers at extrathoracic sites as well. The consistency of an increased cancer risk at extrathoracic sites and its magnitude, either in absolute (observed-expected deaths) or relative (observed/expected deaths) terms, is less for cancer at other sites than for lung cancer. Nevertheless, many occupational studies document significant cancer risks at various GI sites. Cancer of the kidney has also been found to be significantly elevated in two large studies

(Selikoff et al., 1979; Puntoni et al., 1979). Among female workers, ovarian cancer has been found in excess (Newhouse et al., 1972). While no other specific sites have been shown to be elevated at the 0.05 level of significance, the category of all cancers other than lung, GI tract or mesothelial is significantly elevated (Selikoff et al., 1979).

Table VI-1 lists all studies in which more than 10 GI cancers were expected or observed and in which the overall lung cancer risk was elevated at the 0.05 level of significance. This choice eliminated many small studies from consideration, which have statistically uncertain data, as well as several large studies that demonstrated a low risk of lung cancer, either because of exposure or follow-up circumstances. Because the excess risk of GI cancer is less than that of the lung, significantly elevated risks are unlikely to be seen in studies that demonstrate little lung cancer risk. Negative data in such studies do not carry great significance. Data in Table VI-1 show that all but one of the listed studies has an excess GI cancer risk, albeit in three studies the risk is small. However, 5 of the 13 studies demonstrate the risk at a 0.05 level of significance. Figure VI-1 displays the relationship between the relative risk of lung cancer and relative risk of GI cancer in the 12 studies with excess GI cancer risk. A consistent relationship exists between a greater GI cancer risk and an increased lung cancer risk. The GI tract obviously is exposed to fibers because the majority of inhaled fibers are brought up from the respiratory tract and swallowed (Morgan et al., 1975). Additionally, some fibers may become entrapped within the gut wall (Storeygard and Brown, 1977).

TABLE VI-1

Observed and Expected Deaths for Various Causes in Selected Mortality Studies*

Respiratory Cancer ICD 162-164			Digestive Cancer ICD 150-159				Other Cancers				Reference
O	E	O-E	O	E	O-E	$\frac{(O-E)_d}{(O-E)_r}$	O	E	O-E	$\frac{(O-E)_o}{(O-E)_r}$	
63	23.3	39.7	55	39.9	15.1	0.380	55	45.6	9.4	0.237	Henderson and Enterline, 1979
230	184.0	46.0	276	272.4	3.6	0.078	237	217.4	19.6	0.426	McDonald et al., 1980
103	43.2	59.8	40	34.0	6.0	0.100	38	27.4	10.6	0.177	Newhouse and Berry, 1979 (male)
27	3.2	23.8	20	10.2	9.8	0.412	33	20.4	12.6	0.529	Newhouse and Berry, 1979 (female)
93	13.3	79.7	43	15.0	28.0	0.351	28	24.5	3.5	0.044	Selikoff et al., 1979 (NY-NJ)
429	105.6	381.4	122	84.1	37.9	0.099	184	131.8	52.2	0.137	Selikoff et al., 1979 (U.S.)
28	11.0	17.0	10	9.5	0.5	0.029	10	16.1	-6.1	def.	Nicholson et al., 1979
51	23.8	17.2	16	15.7	0.3	0.019	18	24.8	-6.8	def.	Peto, 1977
30	9.8	20.2	15	7.1	7.9	0.527	20	6.8	13.2	0.653	Mancuso and El-attar, 1967
123	54.9	68.1	94	76.6	17.4	0.255	88	81.3	6.7	0.098	Puntoni et al., 1979
83	21.9	61.1	28	22.7	5.3	0.087	39	35.9	3.1	0.037	Seidman et al., 1979
33	9.8	23.2	10	8.1	1.9	0.082	11	14.1	-3.1	def.	Dement et al., 1983
12	3.8	8.2	10	20.3	-10.3	def.	35	39.5	-4.5	def.	Jones et al., 1980

*Source: Adapted from U.S. EPA, 1984

O = observed deaths; E = expected deaths; d = digestive cancer; r = respiratory cancer; o = other cancer; def. = no ratio when deficient in O-E (i.e., O<E)

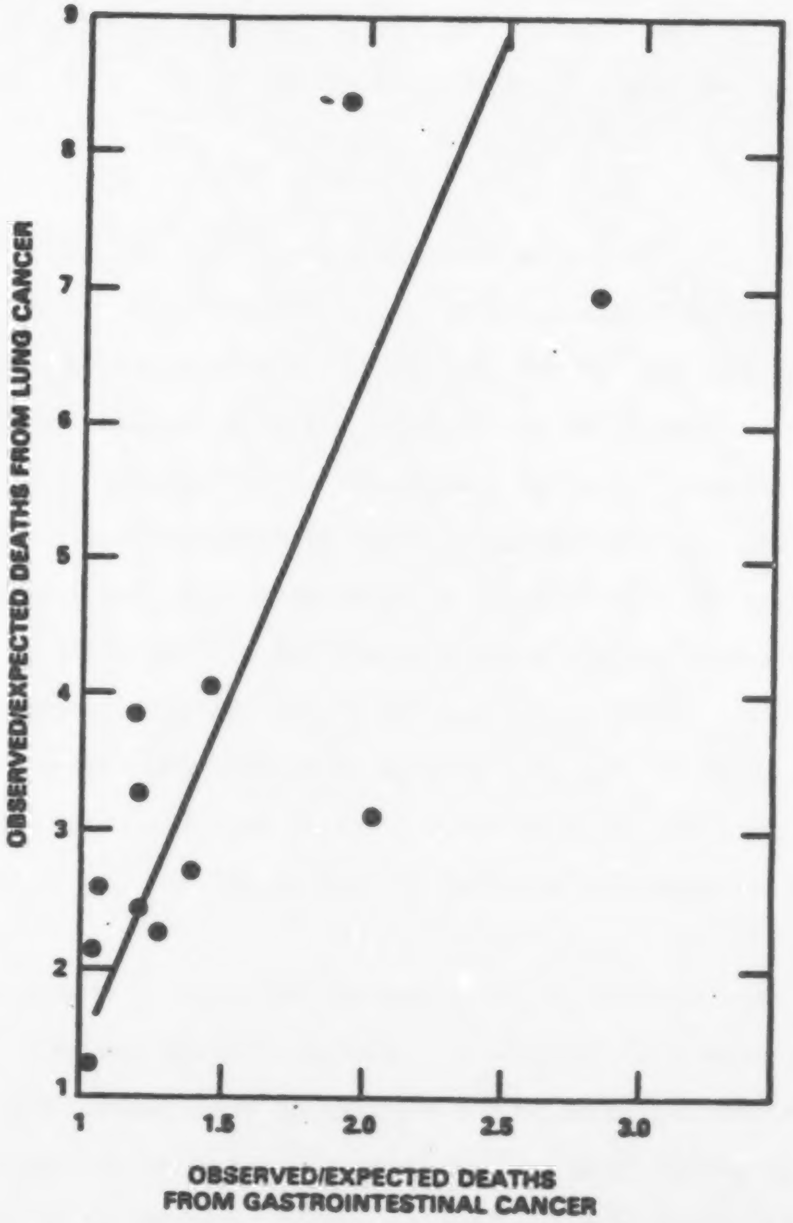

FIGURE VI-1

The ratio of observed to expected mortality from lung cancer versus the ratio of observed to expected mortality from gastrointestinal cancer. [See Table VI-1 for data. The point of Jones et al. (1980) with an SMR of 0.49 for digestive cancer is not plotted.]

Source: U.S. EPA, 1984

Nevertheless, the magnitude of the excess fibers at GI sites is much less than that for the lung. In recent studies, the GI excess is ~10-15% of the lung excess.

Table VI-1 also lists the observed and expected mortality for cancers other than mesothelioma and the GI or respiratory tract. The elevation is not as consistent as that for GI cancer. Only three studies have elevated risks that are significant at the 0.05 level, and deficits are observed in four. The analysis is further complicated by the possibility that misattribution of lung cancer or mesothelioma may have occurred for some cases. For example, brain or liver cancers could be metastatic lung cancers in which the primary cancer was not properly identified. In the study of insulators, Selikoff et al. (1979) found that 26 of 49 pancreatic cancers were misclassified; most of the misclassified were peritoneal mesotheliomas. As with GI cancer, the excess at other sites is much less than the excess for lung cancer and generally less than that for GI cancer.

Unlike the situation of the inhalation of asbestos fibers, no mesothelioma case reports or case control studies document the role of ingested asbestos in drinking water in the etiology of the disease. This may be the result of an overall lower risk of disease from sources of ingested asbestos compared with those from inhaling air around factories or in the homes of workers. Potential cases of mesothelioma caused by ingestion would easily be lost in a background of cases with no attribution. In humans, the only possibility of identifying a carcinogenic effect from ingestion with water is to do large scale epidemiologic studies. Several studies have been published that investigate the possibility of carcinogenic health effects caused by ingested asbestos in six areas of the United States and one in Canada. These areas are Duluth, MN; Connecticut; San Francisco Bay; Utah; Puget Sound; Escambia County, FL and Quebec, Canada.

Epidemiological Studies

The initial concern over the presence of asbestos fibers in drinking water supplies began in 1973 after millions of mineral fibers/ℓ were reported in Lake Superior, the source of municipal water for Duluth, MN and five small communities on the lake shore. It was discovered that the source was the deposition of mine tailings into the lake since 1955. Connecticut offered the possibility of using data collected on asbestos-cement (AC) pipe and linking it with reliable cancer incidence data from the 35+-year-old tumor registry. In the San Francisco Bay area, the sources of several drinking water supplies are acquifers or reservoirs exposed to serpentine rock. In several Utah communities AC pipe was used for periods exceeding 20 years. In addition, Utah is also a member of the Surveillance Epidemiology and End Results (SEER) Program of the National Cancer Institute (NCI) with a complete state-wide tumor registry. In the Puget Sound area of Washington State, three of the largest metropolitan areas have been serviced by water supplies containing chrysotile fibers since the early 1900's. In Escambia County, FL, asbestos fibers were detected in drinking water apparently caused by the deterioration of AC distribution mains that have been used for 30-40 years. Finally, in Quebec, Canada, environmental surveys revealed high concentrations of fibers in drinking water caused by extensive asbestos mining. The studies undertaken in these areas will be briefly described in this chapter. The results are summarized in Tables VI-2 and VI-3.

TABLE VI-2

Summary of Studies of Gastrointestinal Cancer Risk in Relation to Ingested Asbestos by Cancer Site[a,b]

Gastrointestinal Cancer Site	Duluth			Connecticut		Quebec		Bay Area, CA			Utah	Puget Sound, WA		Escambia Co., FL
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
All sites combined	(++)	(--)	(00)	ns	ns	(00)	(+0)	(++)	(++)	(++)	ns	(00)	ns	ns
Esophagus	(+-)	(00)	(00)	ns	ns	(00)	(00)	(0+)	(++)	ns	ns	ns	(00)	(00)
Stomach	(++)	(+0)	(00)	(00)	(00)	(+0)	(+0)	(++)	(++)	ns	(00)	(00)	(00)	
Small intestine	ns	(00)	(00)	ns	ns	ns	ns	(00)	(00)	ns	(00)	ns	(++)	
Colon	(00)	(--)	(00)	(00)	(00)	(00)	(00)	(00)	(+0)	ns	(0-)	(--)	(00)	
Rectum	(++)	(00)	(00)	(00)	(00)	(00)	(00)	(00)	(00)	ns	(00)	ns	(00)	
Biliary passage/liver	(00)	(00)	(00)	ns	ns	ns	ns	(00)	(00)	ns	ns	ns	(00)	ns
Gallbladder	ns	(00)	(00)	ns	ns	ns	ns	(0+)	(00)	ns	(0+)	ns	(00)	ns
Pancreas	(0+)	(++)	(0+)	ns	(+0)	(0+)	(00)	(0+)	(++)	ns	(00)	ns	(00)	(00)
Peritoneum	ns	(00)	(00)	ns	ns	ns	ns	(++)	(0+)	ns	(00)	ns	(00)	ns

[a]Source: Adapted from Marsh, 1983

[b](Male, female) = Association with ingested asbestos: + positive; 0 none; - negative; ns = not studied

1. Mason et al., 1974
2. Levy et al., 1976
3. Sigurdson et al., 1981
4. Harrington et al., 1978
5. Meigs et al., 1980
6. Wigle, 1977
7. Toft et al., 1981
8. Kanarek et al., 1980
9. Conforti et al., 1981
10. Tarter, 1981
11. Sadler et al., 1981
12. Severson, 1979
13. Polissar et al., 1982
14. Millette et al., 1983

TABLE VI-3

Summary of Studies of Nongastrointestinal Cancer Risk in Relation to Ingested Asbestos by Cancer Site[a,b]

Nongastrointestinal Cancer Site	Duluth			Connecticut		Quebec		Bay Area, CA			Utah	Puget Sound, WA		Escambia Co., FL
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Buccal cavity and pharynx	ns	ns	ns	ns	ns	(00)	(00)	ns	ns	ns	ns	ns	(00)	ns
Bronchus, trachea, lungs	(+0)	ns	(00)	ns	(00)	(+0)	(+0)	(+0)	(00)	ns	ns	ns	(00)	(00)
Pleura	ns	ns	ns	ns	ns	ns	ns	(0+)	(0+)	ns	ns	ns	ns	ns
Prostate (males only)	ns	ns	ns	ns	ns	0	0	0	+	ns	ns	ns	+	0
Kidneys	ns	ns	ns	ns	(00)	(00)	(00)	(0+)	(00)	ns	(+0)	(00)	(00)	(00)
Bladder	ns	ns	ns	ns	(00)	(00)	(00)	(00)	(00)	ns	ns	ns	(00)	(00)
Brain/CNS	(00)	ns	ns	ns	ns	(00)	(00)	(00)	(00)	ns	ns	ns	(+-)	ns
Thyroid	ns	ns	ns	ns	ns	ns	ns	(00)	(00)	ns	ns	ns	(++)	ns
Leukemia, aleukemia	(00)	ns	ns	ns	ns	(00)	(00)	(00)	(00)	ns	(+0)	ns	(+-)	ns

[a] Source: Adapted from Marsh, 1983

[b] (Male, female) = Association with ingested asbestos: + positive; 0 none; - negative; ns = not studied

1. Mason et al., 1974
2. Levy et al., 1976
3. Sigurdson et al., 1981
4. Harrington et al., 1978
5. Meigs et al., 1980
6. Wigle, 1977
7. Toft et al., 1981
8. Kanarek et al., 1980
9. Conforti et al., 1981
10. Tarter, 1981
11. Sadler et al., 1981
12. Severson, 1979
13. Polissar et al., 1982
14. Millette et al., 1983

Two studies were initially undertaken to investigate the possible effects of asbestos in the municipal water of Duluth, MN. Mason et al. (1974) reviewed the age-adjusted cancer death rates for Duluth in four periods of time and compared them with those of the State of Minnesota and Hennepin County (Minneapolis). Risk ratios (Duluth/comparison group) were elevated for many GI sites, particularly males. However, higher risk ratios for many sites existed before the water supply was contaminated. The only cancer that showed a consistently increasing risk with calendar periods in both males and females was cancer of the rectum. A study by Levy et al. (1976) compared GI cancer incidence in Duluth with comparable data collected in Minneapolis and St. Paul for the years 1969-1971. Cancer of the stomach in males was significantly greater in Duluth than St. Paul, but not in Minneapolis. Colon/rectal cancer was lower in Duluth than either Minneapolis or St. Paul. The only other cancer site elevated was that of the pancreas for males and females combined.

Sigurdson et al. (1981) continued the follow-up of Duluth residents and compared Duluth rates for 1972-1974 with those of 1969-1971. Mortality rates in Duluth were substantially greater than those of Minneapolis for cancer of the stomach, small intestine and rectum in males and females, and cancer of the pancreas in females, for the years 1969-1971. However, as found in the earlier study by Levy et al. (1976), the corresponding incidence rates for both cities were quite similar. Lung cancer rates significantly increased in females and decreased in males in Duluth between 1969-1971 and 1972-1974. These changes are likely to be related to cigarette smoking habits, rather than the ingestion of the asbestos fibers. In the final study of this series (Sigurdson, 1983) Duluth rates from 1974-1976 were compared with those of 1969-1971. A decrease in cancer of the prostate and an increase in cancer of the pleura were found in males; increases in uterine cancer, multiple myeloma and cancer of the lung were found in females.

Two studies have been conducted of relatively small populations in Quebec that were exposed to exceedingly high concentrations of chrysotile. Unfortunately, the results are in part confounded by occupational and residential exposures to airborne asbestos because of mining activities in the area. The study by Wigle (1977) compared the mortality rates for various causes in individuals ingesting up to 10^9 f/ℓ in water compared with those drinking what was thought to be much lower concentrations of asbestos. Excess cancers of the stomach and lung in males and of the pancreas in females were observed in the two municipalities with extremely high exposures. However, the male mortality was likely to have been from occupational exposure to asbestos. Toft et al. (1981) compared the age-adjusted mortality rates for the communities of Sherbrooke and Thetford Mines with 52 comparison localities believed to have considerably lower asbestos exposures. Stomach and lung cancers were elevated in men at Thetford Mines, presumably from occupational exposures; no elevated risks were found at Sherbrooke, a municipality with high fiber concentrations. The population is relatively small and the comparison analysis is of very low power.

A series of studies have been conducted of the cancer incidence in the San Francisco Bay area, part of which is served by water systems containing concentrations of asbestos up to 36 million fibers/ℓ. The first published report of this research (Kanarek et al., 1980) compared cancer incidence in low (16,000-32,000 f/ℓ), medium (330,000-4,100,000 f/ℓ) and high 5,400,000-36,000,000 f/ℓ) fiber groups of census tracts. Correlation coefficients significant at the $p<0.01$ level were found between chrysotile asbestos water concentrations and white male lung cancer, white female gall bladder cancer, and pancreatic and peritoneal cancer in both sexes. Weaker correlations ($0.01<p\leq 0.05$) were found between asbestos levels and female esophagus, pleura and kidney cancer, as well as stomach cancer in both sexes. A later follow-up (Conforti et al., 1981) extended the observations through 1974 and found a correlation between chrysotile asbestos content and white male cancers of the digestive tract, esophagus, stomach and pancreas. White female cancers of the esophagus, stomach, digestive-related organs and pancreas were also elevated. The associations appeared to be independent of income, education, asbestos occupation, marital status and population mobility. The variables tested, however, were group census data on socioeconomic status and for occupation, the variable was number of construction, electrical and textile workers, as these trades were considered to have a possible occupational exposure to asbestos. A later analysis of Conforti (1983) considered population density as an independent variable and found that consideration of this variable led to slightly more significance for the asbestos regression coefficients that indicated a positive association between ingested chrysotile asbestos and some cancer sites. However, it was the conclusion of the author that population density had little effect on the observation of an association between ingested asbestos and cancer (Conforti, 1983).

One interesting analysis of the correlation between digestive system cancer and asbestos concentrations is that of Tarter et al. (1983). They found that within San Francisco, in the high asbestos exposure areas, there may be two subpopulations, each having a different risk or different risks of GI cancer. The origin of this bimodal response is unclear.

A study by Polissar et al. (1982) found no association between high concentrations of chrysotile asbestos (up to 200 million f/ℓ) and cancer at various digestive sites. However, only 78,000 individuals were served by a water system with such levels. In their initial study, cancer incidence and mortality data for individuals drinking water with high asbestos content were compared with populations having much lower exposures (~7×10^{6} f/ℓ) in other areas. Odds ratios for tumors of the small intestine were consistently elevated in both sexes, as were those for neoplasms of the thyroid, eye, testes and prostate in males. Inasmuch as 332 different odds ratios were calculated, the possibility that these significant elevations occurred by chance is high. The authors did not attribute any of the increases to the asbestos in community water supplies. Subsequently, a case-control study was conducted by Polissar et al. (1983, 1984). Through the western Washington population-based tumor registry, 382 cases were identified as having cancer of the buccal cavity, pharynx, respiratory system, digestive system, bladder or kidney. The control group consisted of 462 individuals. Interviews were conducted with all individuals and validated by secondary sources along with other methods. Estimates of exposure were made based upon information obtained through the interviews. The authors conclude that there was no convincing evidence for cancer risk from ingested asbestos. The exposure between the cases and controls were found to be similar. Of 84 dependent estimates of risk by sex, cancer site and exposure, 63 were found to produce a protective effect and 21 were found to increase risk. The only sites where results might be considered slightly suggestive are male pharynx and male stomach. However, this result is considered to be spurious based on the number of tests made and because the female risks at the same two sites indicate a protective effect.

Millette et al. (1983) studied cancer mortality for the populations in 40 census tracts of Escambia County, FL that have been receiving drinking water through AC pipes for up to 40 years. Cancer mortality data from these 40 census tracts were compared with data from other tracts where AC pipe was not in use. No statistical association was observed between cancer deaths and the use of AC pipe. This is consistent with the finding of Harrington et al. (1978) who studied the use of AC pipe in public potable water supplies and GI cancer incidence in Connecticut for the period 1935-1973. Meigs et al. (1980) also studied AC pipe and cancer incidence in Connecticut but for the period 1955-1974. No associations were observed. Both Connecticut studies investigated age-adjusted, sex-specific incidence data for stomach, colon and rectal cancers.

Three additional studies included in this chapter are reviewed by Marsh (1983). Tarter (1981) offered supportive evidence to the observations by Kanarek et al. (1980) and Conforti et al. (1981) for the San Francisco Bay area. Tarter et al. (1981) observed an increase in all GI cancer sites combined for both males and females. Sadler et al. (1981) investigated associations between cancer incidence and the use of AC pipe in Utah. The only positive associations found were for female gallbladder cancer and male prostate cancer and leukemia/aleukemia. Finally, Severson (1979) investigated cancer mortality in the Puget Sound area. No positive associations were found between cancer and mortality and the asbestos exposure.

In a detailed review of 13 of these studies (Mason et al., 1974; Levy at al., 1976; Sigurdson et al., 1981; Harrington et al., 1978; Meigs et al., 1980; Wigle, 1977; Toft et al., 1981; Kanarek et al., 1980; Conforti et al., 1981; Tarter, 1981; Sadler et al., 1981; Severson, 1979; Polissar et al., 1982) Marsh (1983) includes a lengthy discussion of their limitations. A section of his excellent discussion is included here.

> The large variability in findings evident among the studies is matched by a considerable discrepancy in results for males and females within the 13 studies. Several factors might explain, at least in part, the internal and external inconsistencies in results...the discrepant results may be due to differences in characteristics of asbestos exposure in the various study populations. These differences are summarized in Table VI-4. The relatively low number of positive associations found in Utah and Connecticut could be due to the low concentrations of asbestos in the drinking water or to the relatively short duration of community exposure in several study subareas. The virtual absence of positive findings in the (Sigurdson et al., 1981) Duluth study could also be due to relatively short duration of exposures as well as the amphibole fiber, which is fundamentally different from the chrysotile fibers found in the remaining study areas. By utilizing the differences in exposure characteristics, the three study areas associated with long duration of exposures (>40 years) to chrysotile asbestos can be roughly ranked according to the concentration of fibers in their water systems. However, the resulting ranking, Bay Area (lowest), Puget Sound (intermediate), and Quebec (highest), does not appear to be related to the pattern of associations shown in Tables VI-2 and VI-3.
>
> In addition to duration and intensity, it is also likely that other exposure factors, such as the characteristics of asbestos

TABLE VI-4

Characteristics of Asbestos Exposures in Drinking Water in Various Study Populations[a]

Characteristic	Duluth, MN	Connecticut	Quebec	Bay Area, CA	Utah	Puget Sound, WA
Type of asbestos	amphibole	chrysotile	chrysotile	chrysotile	chrysotile	chrysotile
Number of fibers/ℓ[b,c]	$1.0\text{-}30.0\times10^{-6}$	$\text{BDL-}0.7\times10^{-6}$	$1.1\text{-}1300\times10^{-6}$	$0.025\text{-}36\times10^{-6}$	NA[c]	$7.3\text{-}206.5\times10^{-6}$
Population exposed	100,000	576,800	420,000	3,000,000	24,000	200,000
Maximum duration of exposure, year	15-20	23-44	>50	>40	20-30	>40

[a] Source: Adapted from Marsh, 1983

[b] BDL = Below detectable limit

[c] NA = Data not available

pipe used, the concentration of other possibly carcinogenic contaminants of water, and certain physical properties of asbestos fiber (e.g., length), vary among and within the six study areas.

As a second major factor, the different study designs employed in the various areas, coupled with the disparity in their underlying strengths and weaknesses, most likely also contributed to the observed variability in results. The most important methodologic weaknesses and limitations ascertained from the individual reviews are summarized in Table VI-5. The weaknesses are listed in approximate decreasing order of importance relative to their potential impact on the credibility and definitiveness of the findings.

By far the most serious limitation of all the studies conducted to date is that they are ecological or, more specifically, geographic correlation studies by design. This drawback alone does not permit a definitive conclusion to be made from any of the studies of the possible adverse health effects of ingested asbestos. The major drawback of ecological analysis for testing etiologic hypotheses is the potential for substantial bias in effect estimation. This problem, known as the "ecological fallacy," results from making a causal inference about individual phenomena on the bias of observations of groups. Theoretically, the bias resulting from ecological analysis can make an association appear stronger or weaker than it is at an individual level; however, in practice, this bias ordinarily exaggerates the magnitude of a true association, if one exists (Langbein and Lichtman, 1978; Duncan et al., 1961; Valkonen, 1969). Ecologic study bias can be minimized, for example, through the judicious application of ecologic regression techniques. Such techniques were employed, at least in part, in the Connecticut study of Meigs et al. (1980), the three Bay Area studies, and the two Puget Sound studies. However, the overall variability in results does not appear to be any less among or within these six studies compared to the remaining seven, which did not incorporate more refined ecologic analyses.

TABLE VI-5

Summary of Methodologic Weaknesses and Limitations Associated with Various Studies of Ingested Asbestos[a,b]

Weakness/limitation[c]	Duluth			Connecticut		Quebec		Bay Area, CA			Utah	Puget Sound, WA		Total Across Studies
	1	2	3	4	5	6	7	8	9	10	11	12	13	
Ecologic study design	*	*	*	*	*	*	*	*	*	*	*	*	*	13
Insufficient latency period	*	*	*	-	-	-	-	-	-	-	*	-	-	4
Death certificate data	*	-	-	-	-	*	*	-	-	-	-	-	-	3
Duration and/or intensity of exposure low	*	*	*	*	*	-	-	-	-	-	*	-	-	6
Uncontrolled confoupding														
Race	-	*	*	*	*	*	*	-	-	*	*	*	*	10
Sex	-	-	-	-	-	-	-	-	-	*	-	-	-	1
Occupation	*	*	*	*	*	*	*	-	-	*	*	*	-	10
Socioeconomic status	*	*	*	*	-	*	*	-	-	*	-	-	-	7
Population density	*	*	*	-	-	*	*	*	*	*	-	*	*	10
Ethnicity	*	*	*	*	*	*	*	-	-	*	*	*	*	11
In/out migration	*	*	*	*	*	*	*	-	-	*	-	-	-	8
Personal habits	*	*	*	*	*	*	*	*	*	*	*	*	*	13
Absence (or incomplete) data on dose-response	*	*	*	*	*	-	-	-	-	-	*	*	*	8
Multiple comparisons problem	*	*	*	*	*	*	*	*	*	-	*	*	*	12
Insensitivity of summary statistics	*	*	*	*	*	-	-	*	*	*	-	*	*	10
Absence of historical asbestos exposure data	*	*	*	*	*	*	*	*	*	*	*	*	*	13
Use of at least one questionable statistical procedure	-	*	-	-	*	-	-	*	*	-	-	-	-	4
Total	14	15	14	12	12	11	11	7	7	11	10	10	9	

[a] Source: Adapted from Marsh, 1983

[b] Legend asterisk (*) indicates presence of characteristic; minus (-) indicates absence of characteristic

[c] In approximate decreasing order of relative impact on definitiveness of study results

1. Mason et al., 1974
2. Levy et al., 1976
3. Sigurdson et al., 1981
4. Harrington et al., 1978
5. Meigs et al., 1980
6. Wigle, 1977
7. Toft et al., 1981
8. Kanarek et al., 1980
9. Conforti et al., 1981
10. Tarter, 1981
11. Sadler et al., 1981
12. Severson, 1979
13. Polissar et al., 1982

Much of the bias inherent in ecologic analysis results from the inability to control for confounding factors at the individual level. Table VI-5 shows that most of the studies reviewed did not directly control for confounding factors even at the group level. Notable exceptions are the Bay Area studies of Kanarek et al. (1980) and Conforti et al. (1981) and the two Puget Sound studies, which employed relatively more sophisticated multivariate statistical analyses as an attempt to control for confounding at the group level. Only one study to date, that of Polissar et al. (1982), attempted to collect data on a confounding variable at the individual level; however, since this was done only for cancer cases and not controls, it was not possible to analyze the data on a more sensitive and reliable case-control basis.

Occupation was a particularly important confounding variable in the studies conducted in Quebec, the Bay Area, and Connecticut, since a substantial number of males are employed in the various asbestos-related industries within these areas. The confounding effects of occupation are particularly evident in the two Quebec studies, where positive associations for lung and stomach cancer were consistently confined to males.

Misclassification of asbestos exposures is another serious limitation of all the studies conducted to date. This misclassification results from several factors including: the basic ecologic design, which assigns specific exposures to an entire geographic area; tenuous assumptions regarding the extent of asbestos contamination from asbestos pipes; the lack of any reliable historical asbestos exposure data; and the in/out and daily mobility of the study populations.

It is also likely that many of the associations found among the 13 studies are simply chance occurrences arising from the large number of statistical comparisons that were generally made. Whenever a large number of significance tests are performed at a constant significance level, a certain number of tests will be significant by chance alone and the actual significance levels must be higher than those reported by the authors. Among the 13 studies reviewed, the number of separate statistical comparisons reported ranged from 33 to 336 with an average of 193. Therefore, at a 5% level of significance, the number of positive findings expected due to chance alone would range from approximately 2 to 17 with an average across the 13 studies of about 10. In other statistical terms, the probability that at least one of the n independent comparisons was due to chance alone ranged from 0.81 in a study reporting about 30 comparisons to virtual certainty in studies reporting 100 or more comparisons. (At the 5% level of significance, the probability of falsely claiming statistical significance in at least one of n independent comparisons is $1-0.95^n$.)

Marsh (1983) also conducted a probability analysis of eight independent studies (Mason et al., 1974; Sigurdson et al., 1981; Meigs et al., 1980; Wigle, 1977; Toft et al., 1981; Conforti et al., 1981; Sadler et al., 1981; Polissar et al., 1982) attempting to associate increased cancer risk with asbestos exposure. He considered whether the observed positive associations in males and females for neoplasms at various GI sites were likely to have been generated by chance, and found that those of the esophagus, stomach, pancreas and prostate may have a biological basis related to ingested asbestos. Marsh treated each independent study equally, even though studies of Connecticut were severely limited by the low asbestos concentrations in the study area, and the study of Utah was limited by a very small exposed population. Were these studies to be excluded from his analysis, the strength of positive findings would be increased.

In a review of Table VI-2 it can be seen, as was demonstrated analytically by Marsh (1983), that the possibility of an elevated risk of cancer of the stomach and pancreas must be considered as possibly associated with ingestion of asbestos in water. The stomach is an obvious site for concern as this cancer rate has been shown to be elevated in several studies of occupationally-exposed workers. Cancer of the pancreas has not been directly implicated as a site of elevated cancer risk from exposure to asbestos through inhalation. However, a large number of peritoneal mesotheliomas have been misclassified as cancers of the pancreas (Selikoff et al., 1979) and, in the absence of complete pathological review, an increase in pancreatic cancer may be the result of an increase in peritoneal mesothelioma. The finding of an elevated cancer risk of the peritoneum in San Francisco and, perhaps in Duluth, also is suggestive.

All of the studies discussed, with the exception of Polissar et al. (1983, 1984) are limited because of their ecological design. Group data are utilized for exposure estimates and for possible confounding variables. One of the most serious of confounding factors is that of possible occupational exposure to asbestos. Nicholson et al. (1979) estimated that 20 million individuals in the United States may have had employment in an industry with possible exposure to asbestos. More than 4 million are known to have had previous shipyard employment where asbestos risks are high. Studies by Blot et al. (1978) suggested that employment in a shipyard for as short as 2-3 years increases the risk of lung cancer by 60%. A study by Puntoni et al. (1979) demonstrated an elevated risk of lung cancer (O/E=2.24), cancer of the stomach (O/E=1.36) and cancer of the colon (O/E=1.81). The San Francisco Bay area was one of the most important ship-building regions of the United States, and many current residents would be expected to have had past employment in one of the Bay areas yards. Further, the SEER Program indicates that the mesothelioma mortality experience in the Bay area is one of the highest in the United States (NAS, 1984). The possible confounding effect of occupational exposures requires that a definitive analysis of cancer risk in the Bay area explicitly take into account occupation on an individual basis. This would suggest a case control study of cancers of the esophagus, stomach, pancreas and perhaps colon and rectum. The study design should be prospective and incorporate in the protocol the interviewing of individuals at the time of diagnosis, so that occupational and other relevant histories can be taken from the individual in question rather than from relatives. It should also include a pathological review of all tissue material available on pancreatic cancers in order to ascertain whether misclassification of mesothelioma has occurred.

High-Risk Subpopulations

Hypersusceptible individuals have not been defined for ingested exposures to mineral fibers. It is well known that smokers exposed to asbestos dusts from inhalation are at a higher risk of developing lung cancer than are nonsmokers with similar exposures (Hammond et al., 1979). This phenomenon has not been demonstrated to also apply to the ingestion of asbestos. Since it is theorized that ingested asbestos may result in increased cancers of the digestive system, one would expect that persons with pre-existing diseases, ailments or risk factors associated with the digestive system would be more susceptible to the carcinogenic potential of ingested asbestos. However, no such data were found in the available literature. This is an area requiring further research.

Summary

Acute exposures to ingested asbestos fibers in humans have resulted in the detection of fibers in body fluids that has not been associated with specific health effects. Chronic exposures have not resulted in nonmalignant effects; however, several studies have been performed to investigate the carcinogenic potential of chronic exposure to ingested asbestos on human populations. The results of these studies are summarized in Tables VI-2 and VI-3.

The possibility of an elevated risk of cancer of the stomach and pancreas must be considered as possibly associated with ingestion of asbestos in water. However, this conclusion is based on a number of epidemiological studies with several limitations. Additional research is needed in this area.

VII. MECHANISMS OF TOXICITY

Investigation on the mechanism of ingested asbestos toxicity has concentrated on the effects of asbestos in the gut. Research has been conducted *in vivo* and *in vitro*.

Toxicity

Jacobs et al. (1977) reported changes in the DNA, RNA, protein and some enzyme activities in the small intestine mucosal lining cells and gut lumen, induced by maintaining rats on a diet containing chrysotile asbestos. Test groups of six rats were fed chrysotile asbestos at 0.5 mg asbestos/day or 50 mg asbestos/day both pretreated with cigarette smoke and in the absence of cigarette smoke for a period of 10 months. Control groups (also six rats) received either commercially available rat pellets or rat pellets pretreated with cigarette smoke.

Results of this study reveal that persistent ingestion of asbestos in the diet induced some changes in the gut mucosal lining cells, but greater alterations were detectable in the levels of macromolecules in the lumen of the small intestine. The levels of RNA in the lumen were significantly lower and DNA significantly higher in all groups of animals ingesting asbestos (irresponsive of cigarette smoke pretreatment) compared with control animals. These alterations of macromolecules in the lumen were judged to be consistent with a mineral-induced cytotoxicity. Most intracellular enzyme levels were consistently, but not significantly, elevated in animals maintained on asbestos diets. Enzyme activities within the lumen were significantly higher in exposed animals compared with controls.

In a follow-up study, Jacobs et al. (1978b) reported a significant increase in the incorporation of [^{3}H]-thymidine into DNA in the small intestine mucosa, colon, rectum, stomach and spleen of rats that had ingested 50 mg/day chrysotile in both the short- (1 week) and long-term (5-15 months) experiments. This work provides supporting evidence that ingestion of chrysotile asbestos interferes with DNA metabolism in rat tissues in the GI tract and other body organs. In more recent work, Jacobs and Richards (1980) monitored the distribution of [^{3}H]-sucrose and its radiolabeled degradation products in isolated perfused small intestine loops of rats that had previously ingested chrysotile (50 mg/day) for 10 weeks. They discovered lower levels of radiolabeled glucose in these rats and argued that cytotoxic action of chrysotile on mucosal cells was such that active transport of glucose across the membrane was impaired.

Donham et al. (1980) studied the effects of ingested asbestos on the colon of weanling F344 rats. Based on results of preliminary experimentation, the dosage was established at 10% by weight of a standard laboratory diet. Two hundred forty animals comprised the test group; there were also 242 control rats fed 10% nonnutritive cellulose and a group of 121 controls was fed normal laboratory chow. The study was terminated at 32 months. Epithelial tumors of the colon (8 adenocarcinomas and 1 adenoma) were found in nine of the rats. Four tumors were in asbestos-fed rats, two tumors in the nonnutritive cellulose-fed group, and three tumors were found in the standard laboratory diet controls. Also, one malignant mesothelioma was found in the asbestos-fed group. Although the differences in the numbers of tumors between asbestos-fed animals and controls were not significant, the authors believe their experimentation suggests that ingested asbestos is not inert in the colon. Included in their results is the discovery that cyclic-AMP levels in the colon were significantly lower in asbestos-fed animals vs. controls.

Cellular Effects

In vitro tests have been studied to define asbestos-induced cellular responses and their possible relationship to neoplasia in GI and respiratory epithelium (Mossman, 1983; Daniel, 1983). The fibers interact with mucosal cells. The biological activity is determined by surface charge, crystallization and dimensional characteristics along with adsorption of natural secretions and serum components to fibers that ameliorate cytotoxicity. Observing such interactions, Mossman (1983) concluded that asbestos fibers appear to be epigenetic carcinogens and that the role of asbestos fibers in carcinogenicity in respiratory epithelium can be compared with that of classical tumor promoters. This is supported by the fact that various types of asbestos do not cause single-strand breakage of DNA in human and hamster respiratory epithelial cells. In addition, various asbestos fibers are not mutagenic in a number of cell types (Daniel, 1983). Finally, unless combined with PAH, asbestos is not carcinogenic in hamster tracheal implants (Mossman and Craighead, 1978) and is only weakly carcinogenic in rats following repeated intratracheal instillations (Mossman and Craighead, 1981). Daniel (1983) concludes that while asbestos fibers are clastogenic to cultured rodent cells, there is little other evidence for genotoxicity of fibers. Thus, as stated by Daniel (1983), although fibers may act at the stage of tumor initiation (gene toxicity) by means of a clastogenic event, it may be more reasonable to look at other mechanisms such as cocarcinogenesis or promotion for the oncogenic potential of these mechanisms.

Reiss et al. (1980a) demonstrated the cytotoxic action of asbestos on various mammalian cell lines in vitro. Amosite, crocidolite and chrysotile asbestos were assayed for their cytotoxicity using embryonic human intestine-derived (I-407) and adult rat liver-derived (ARL-6) epithelial cells in culture. The order of cytotoxicity was chrysotile > amosite > crocidolite. All three types of asbestos were more toxic to I-407 than to ARL-6 cells. These asbestos types were also tested for inhibition of colony formation in cultures of mouse colon-derived epithelial-like cells (MCE-1). These cells were more resistant than I-407 to all three asbestos types. MCE-1 was similar to ARL-6 cells in response to chrysotile and amosite; MCE-1 cells were more sensitive to crocidolite than were ARL-6 cells.

Other recent evidence is available demonstrating the effects of asbestos on cellular membranes. Jaurand et al. (1979) investigated the effects of exposure of human erythrocytes (red blood cells) to asbestos fibers. Asbestos fibers (chrysotile and crocidolite or both) and erythrocytes were pre-incubated separately for 10 minutes at 37°C. For time periods up to 60 minutes, 1 mℓ of each suspension was mixed together and incubated at 37°C. At the end of the exposure period samples were centrifuged 10 minutes at 1200 x g and optical density was determined at 540 nm. Results were expressed as percent of hemolysis. Complete hemolysis was obtained by addition of 0.2% (v/v) Triton X-100 to the erythrocyte suspension.

Examination of the kinetics of hemolysis in an isotonic medium with various concentrations of red blood cells and fibers revealed that maximal hemolysis depended on the relative concentrations of chrysotile and erythrocytes, not on the absolute concentration. A 10-fold increase in the absolute concentrations of each (e.g., 0.5 mg $m\ell^{-1}$ chrysotile and 0.5% red blood cells up to 5 mg $m\ell^{-1}$ chrysotile and 5% red blood cells) resulted in the same kinetics and final level of hemolysis. These results indicate that hemolysis of erythrocytes by chrysotile is a self-inhibiting process. Microscopic studies showed that the effect of asbestos on red blood cells is not a rupture of the cells but a progressive increase in membrane permeability. The cells lose hemoglobin, gradually become ghosts, and subsequently disappear into the bundles of fibers. In this study Jaurand et al. (1979) demonstrated a clear relationship between maximal hemolysis and the relative surface areas of chrysotile and red blood cells in the medium. They assumed that the inhibition of hemolysis by asbestos fibers is attributable to binding of red cell membrane components, either lipids or protein, or both. This assumption was verified by preincubating asbestos fibers with red cell ghosts or liposomes made either of dipalmitoyl phosphatidylcholine alone or a mixture of lipids. This preincubation step prevented subsequent hemolysis of red cells. Therefore, it was concluded that the effect of chrysotile on red cells is at least partly, if not completely, attributable to lipid extraction and adsorption onto the fibers.

Other studies have demonstrated effects of asbestos on cellular membranes. Newman et al. (1980) reported that asbestos has no independent mutagenic capability in testing of Syrian hamster embryo cells but asbestos affects surface membrane glycolipids and glycoproteins possibly increasing membrane permeability and allowing other mutagens into the cell (see Chapter VI).

Synergistic Effects

The effects of asbestos fibers on cellular membrane permeability has led some investigators to explore possible synergistic effects between asbestos and other substances.

Some studies have demonstrated effects of asbestos on BaP transport and metabolism, especially transfer of the carcinogen from the surface of particulate material to rat liver microsomes, microsomal membranes and lipid micelles (Lakowicz and Bevan, 1980; Kadaswami and O'Brien, 1980; McLemore et al., 1979; Hart et al., 1980; Brown et al., 1983; Mossman and Craighead, 1981). Asbestos mediates a rapid transport of BaP across cellular membranes and this enhanced availability may be a significant factor in the cocarcinogenesis between particulate material and PAHs. Asbestos appears to alter BaP metabolism and activity of aryl hydrocarbon hydroxylase. The relevance of these factors to ingested asbestos has not been established.

Some evidence of synergistic effects of asbestos on other agents was provided by Kanazawa et al. (1979). They administered 5 μg/mℓ asbestos plus 10^5 FFU/mℓ Moloney murine sarcoma virus i.p. in CBA mice and observed for 100 days. Palpable intraperitoneal tumors were observed in 72.1% of mice receiving asbestos and virus while 1 of 59 mice developed similar tumors with virus alone; no tumors were reported in mice receiving asbestos only.

Most authors caution that more work needs to be done in this area. As noted, all studies were conducted with animals or *in vitro* and no controlled human studies have been conducted. At this time, the elucidation of the mechanism of toxicity of ingested asbestos in humans is based upon extrapolation from animal or *in vitro* research.

Studies relevant to this chapter are listed and summarized in Table VII-1.

Summary

Asbestos has been demonstrated to interfere with DNA metabolism in rat tissues of the GI tract and other organs. In addition, impaired active transport of glucose across membranes and other cytotoxic effects have been associated with asbestos exposure. Specifically, chrysotile exposure has resulted in the hemolysis of erythrocytes. The effect of chrysotile on red blood cells may be attributed to lipid extraction and adsorption onto fibers.

Asbestos may act as a cocarcinogen with BaP and Maloney murine sarcoma virus. Asbestos mediates transport of BaP across cell membranes and may alter BaP metabolism. A greater number of tumors were seen in animals receiving asbestos + virus than seen in animals receiving asbestos or virus alone. Additional work is needed in this area.

TABLE VII-1

Studies Relevant to Mechanisms of Asbestos Toxicity

Species	Route of Exposure	Dose	Results	Reference
Toxicity				
Rat (male, MRC hooded)	ingestion	0.5-50 mg/day for 10 months	At both doses, asbestos induced some changes in the gut mucosal lining cells. The lumen of the small intestine had significantly increased DNA and significantly decreased RNA levels. Enzyme activity was high in the lumen. β-glucuronidase activity was higher in mucosal cells.	Jacobs et al., 1977
Rat (male, MRC hooded)	ingestion	50 mg/day for 1 week or 5-15 months	Asbestos interfered with DNA metabolism in the GI tract. A significant increase in the incorporation of [^{3}H]-thymidine into DNA was observed.	Jacobs et al., 1978b
Rat (MRC hooded, sex not specified	ingestion	50 mg/day for 10 weeks	Distribution of ^{3}[H]-sucrose and its radiolabeled degradation products was monitored. Statistically significant lower levels of radiolabeled glucose in asbestos-fed rats may relate to the cytotoxic action of chrysotile on mucosal cells such that the energized carrier mechanism that transports this sugar is impaired.	Jacobs and Richards, 1980
Rat (weanling F344, 304M, 299F both	ingestion	The principal exposure group was fed a 10% asbestos diet. A fiber control group was placed on a diet containing 10% non-nutritive cellulose. A second control group was placed on a standard lab diet.	Weanling F344 rats, fed a diet containing 10% chrysotile (B), were studied over their lifetime to determine the effects of ingested asbestos on the colon. Epithelial tumors of the colon (8 adenocarcinomas and 1 adenoma) were found in 9 of the rats under study. Four of the tumors were in asbestos-fed rats, 2 tumors were found in non-nutritive cellulose controls and 3 tumors were found in the standard laboratory rat diet controls. In addition, 1 malignant mesothelioma was found in the asbestos-fed group. Although differences in numbers of tumors between asbestos-fed and control rats were not statistically significant, the authors believe their evidence suggests that ingested asbestos is not inert in the colon. Included in this evidence is the fact that cyclic-AMP levels in colon tissues were significantly lower in asbestos-fed animals compared with controls.	Donham et al., 1980

TABLE VII-1 (cont.)

Species	Route of Exposure	Dose	Results	Reference
Cellular Effects				
Human embryonic intestine-derived (I-407) epithelial cells	*in vitro*	5×10^{-9}% 10^{-1}% solution for 0-7 days	The order of cytotoxicity was chrysotile > amosite > crocidolite.	Reiss et al., 1980a
Rat liver-derived (ARL-6) epithelial cells	*in vitro*	5×10^{-9}% 10^{-1}% solution for 0-7 days	All 3 asbestos types were more cytotoxic to I-407 than to ARL-6 cells, but MCE-1 cells were more resistant than the I-407 cells.	Reiss et al., 1980a
Mouse colon-derived epithelial-like (MCE-1) cells	*in vitro*	5×10^{-9}% 10^{-1}% solution for 0-7 days	Leaching all 3 asbestos fibers in sterile deionized water or hydrochloric acid altered the composition of the fibers (release of Mg^{2+} and Ca^{2+}).	Reiss et al., 1980a
P388D1 macrophage-like cells	*in vitro*	10, 50 or 100 $\mu g/cm^2$ up to 72 hours	Fiber-induced cytotoxicity to the P388D1 cells has been demonstrated to parallel the probability that the fiber will induce a pleural sarcoma in rats. Effect is independent of the chemical nature of the fiber and correlates best with fibers 8 μm in length and with diameters in the range of 0.5-1.0 μm (Stanton hypothesis).	Lipkin, 1980
Human red blood cells	*in vitro*	0.1-5 mg/mℓ for 60 minutes	Hemolysis results from an increase in membrane permeability and not from rupture of red blood cells. The fibers extract and adsorb lipids.	Jaurand et al., 1979
Synergistic Effects				
Rat liver microsomes	*in vitro*	-	Study demonstrated particulate-enhanced availability of BaP to rat liver microsomes when BaP is adsorbed to asbestos.	Lakowicz and Bevan, 1980
Rat or rabbit liver microsomes	*in vitro*	-	Asbestos mediates a rapid transport of BaP into the membrane of rat liver microsomes and impairs BaP metabolism by inhibiting aryl hydrocarbon hydroxylase.	Kandaswami and O'Brien, 1979
CBA mice (3-week-old, both sexes)	i.p.	5 μg/mℓ plus 10^5 FFU/mℓ of Moloney murine sarcoma virus. Observed for up to 100 days.	72.1% of mice developed palpable i.p. tumors, and 50% of these died within 100 days. Only 1 of 59 mice developed similar tumors with the virus alone and no tumors were encountered in mice treated with asbestos alone. The neoplasms appeared to be anaplastic sarcoma and were mostly confined to the serosal surface of the abdominal cavity.	Kanzazwa et al., 1979

VIII. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

The quantification of toxicological effects of a chemical consists of an assessment of the noncarcinogenic and carcinogenic effects. In the quantification of noncarcinogenic effects, an ADI is calculated. The AADI and HA values for the chemical are then calculated to define the appropriate drinking water concentrations to limit human exposure. For ingestion data, this approach is illustrated as follows:

$$\text{ADI} = \frac{\text{(NOAEL or LOAEL in mg/kg/day) (bw in kg)}}{\text{Uncertainty/Safety Factor}} = \text{mg/day}$$

$$\text{AADI} = \frac{\text{ADI}}{\text{Drinking water volume in } \ell\text{/day}} = \text{mg/}\ell$$

where: NOAEL = no-observed-adverse-effect level
LOAEL = lowest-observed-adverse-effect level
Body weight = 70 kg for adult or 10 kg for child
Drinking water volume = 2 ℓ/day for adults or 1 ℓ/day for children

Uncertainty/Safety Factor = 10, 100 or 1000

Utilizing these equations, the following drinking water concentrations are developed for noncarcinogenic effects:

1. A 1-day HA for 10 kg child
2. A 1-day HA for 70 kg adult
3. A 10-day HA for 10 kg child
4. A 10-day HA for 70 kg adult
5. A lifetime AADI for a 70 kg adult

The distinctions made between the HA calculations (items 1-4) are associated with the duration of anticipated exposure. Items 1 and 2 assume a single acute exposure to the chemical. Items 3 and 4 assume a limited period of exposure (possibly 1-2 weeks). The HA values will not be used in establishing a drinking water standard for the chemical. Rather, they will be used as informal scientific guidance to municipalities and other organizations when emergency spills or contamination situations occur. The AADI value (item 5) is intended to provide the scientific basis for establishing a drinking water standard based upon noncarcinogenic effects.

A NOAEL or LOAEL is determined from animal toxicity data or human effects data. For animal data, this level is divided by an uncertainty factor because there is no universally acceptable quantitative method to extrapolate from animals to humans. The possibility must be considered that humans are more sensitive to the toxic effects of chemicals than are animals. For human data, an uncertainty factor is also used to account for the heterogeneity of the human population in which persons exhibit differing sensitivities to toxic chemicals. An Office of Drinking Water (ODW) modification of the guidelines set forth by the National Academy of Sciences (NAS, 1977, 1983) are typically used in establishing uncertainty factors as follows:

- An uncertainty factor of 10 is used when good acute or chronic human exposure data are available and supported by acute or chronic toxicity data in other species.
- An uncertainty factor of 100 is used when good acute or chronic toxicity data identifying NOEL/NOAEL are available for one or more species, but human data are not available.
- An uncertainty factor of 1000 is used when limited or incomplete acute or chronic toxicity data are available or when only the acute or chronic toxicity data identifying a LOAEL (but not NOEL/NOAEL) for one or more species are available.

The uncertainty factor used for a specific risk assessment is judgmental. Factors that cannot be incorporated in the NAS/ODW guidelines (NAS, 1977) for selection of an uncertainty factor, but must be considered, include the following: 1) the quality of the toxicology data, 2) the significance of the adverse effect, and 3) the existence of counterbalancing beneficial effects.

If toxicological evidence requires the chemical to be classified as a potential carcinogen (however, there is insufficient evidence to classify asbestos as a carcinogen following oral exposure), mathematical models are used to calculate the estimated excess cancer risks associated with the ingestion of the chemical by drinking water. The bioassay data used in these estimates are from animal experiments. In order to predict the risk for humans, these data must be converted to an equivalent human dose. This conversion includes correction for noncontinuous animal feeding, nonlifetime studies and for the difference in size. The factor that compensates for the size difference is the cube root of the ratio of the animal and human body weights. It is assumed that the average human body weight is 70 kg and that the average human consumes 2 ℓ of water per day. The multistage model is then fit to the equivalent human data to estimate the risk at low doses. The upper 95% confidence limit of this estimate is used. Excess cancer risks can also be estimated using other models such as the one-hit model, the Weibull model, the logit model and the probit model. There is no basis in the current understanding of the biological mechanisms involved in cancer to choose among these models. The estimates of low doses for these models can differ by several orders of magnitude.

The scientific data base used to calculate and support the setting of risk rate levels has an inherent uncertainty. This is because the tools of scientific measurement, by their very nature, involve both systematic and random error. In most cases, only studies using experimental animals have been performed. There is thus uncertainty when the data are extrapolated to humans. When developing risk rate levels, several other areas of uncertainty exist, such as 1) incomplete knowledge concerning the health effects of contaminants in drinking water, 2) the impact of test animal age, sex and species and the nature of target organ systems examined on the toxicity study results, and 3) the actual rate of exposure of internal targets in test animals or humans. Dose-response data are usually only available for high levels of exposure, not for the lower levels of exposure for which a standard is being set. When there is exposure to more than one contaminant, additional uncertainty results from a lack of information about possible synergistic or antagonistic effects.

Existing Guidelines and Standards

The current Occupational Safety and Health Administration (OSHA) standard for an 8-hour TWA occupational exposure to asbestos is 2 fibers longer than 5 microns in length/mℓ of air (2 f/mℓ or 2,000,000 f/m^3). Peak exposures of up to 10 f/mℓ are permitted for no more than 10 minutes (Federal Register, 1975). This standard has been in effect since July 1, 1976, when it replaced an earlier one of 5 f/mℓ (TWA). In Great Britain, a value of 1 f/mℓ is now the accepted level for chrysotile. This standard resulted from recommendations made in 1979 by the Advisory Committee (1979), which also recommended a TWA of 0.5 f/mℓ for amosite and 0.1 f/mℓ for crocidolite (U.S. EPA, 1984). The previous standard, in effect from 1969 to

1983, was 2 f/mℓ (TWA) (BOHS, 1968). This earlier British standard, in fact, served as a guide for the OSHA standard (NIOSH, 1972).

The British standard was developed specifically to prevent asbestosis among working populations; data were felt to be lacking that would allow for determination of a standard for cancer (BOHS, 1968). Unfortunately, among occupational groups, cancer is the primary cause of excess death for workers with three-fourths or more of asbestos-related deaths caused from malignancy. This fact led OSHA to propose a lower TWA standard of 0.5 f/mℓ (500,000 f/m^3) (Federal Register, 1975). NIOSH, in its criteria document for the hearings on a new standard, has proposed a value of 0.1 f/mℓ (NIOSH, 1976). In the discussion of the NIOSH proposal, it was stated that the value was selected on the basis of the sensitivity of analytical techniques using optical microscopy and that 0.1 f/mℓ may not necessarily protect against cancer. Recognition that no information exists that would define a threshold for asbestos carcinogenesis was also contained in the preamble of the OSHA proposal. The OSHA proposal has been withdrawn and a new proposal is anticipated (U.S. EPA, 1984). NIOSH has reaffirmed its proposal of an 0.1 f/mℓ standard (NIOSH, 1980).

The existing federal standard for asbestos emissions into the environment prohibits either no visible emissions or employment of specified control techniques (U.S. EPA, 1975). No numerical value was specified because of difficulty in monitoring ambient air asbestos concentrations in the ambient air or in stack emissions. Some local government agencies, however, may have numerical standards (e.g., New York, 27 ng/m^3).

No standards for asbestos in foods or beverages exist even though the use of filtration of such products through asbestos filters has been a common practice in past years. Asbestos filtration, however, is now prohibited or limited for human drugs (U.S. FDA, 1976).

The recommended water quality criterion for asbestos particles calculated to keep the individual lifetime cancer risk below 10^{-5}, is 300,000 fibers of all sizes/ℓ. The corresponding mass concentration for chrysotile asbestos is ~0.05 μg/ℓ (U.S. EPA, 1980). The National Academy of Sciences (NAS, 1983) has also calculated the relative risk associated with the ingestion of 110,000 fibers/ℓ of asbestos fibers from drinking water based on inhalation exposure. This criterion is derived from the data that exists for the increased incidence of peritoneal mesothelioma and GI tract cancer in humans exposed occupationally to asbestos. This derivation assumes that much or all of this increased disease incidence is caused by fibers ingested following clearance from the respiratory tract. Several studies suggest the association of proximate airborne fiber concentrations to which individuals were exposed with observed excess peritoneal and GI cancer. All of the inhaled asbestos is assumed to be eventually cleared from the respiratory tract and ingested.

Noncarcinogenic Effects and Quantification of Noncarcinogenic Effects

Very few studies were found in the available literature that investigated the toxic effects following the ingestion of asbestos fibers. However, the limited data suggest that the general toxicity following the ingestion of asbestos is minimal in both animals and humans with no specific target organ defined. This is in sharp contrast to the range of toxic effects seen following exposure by inhalation to asbestos particles; the most severe being asbestosis. The only toxic effects reported in animals following ingestion were changes in the muscosal lining cells of the ileum along with changes in the colon, rectum and small intestine of rats given either 0.5 or 50 mg/day for 1 week or 14 months. No toxic effects were reported in rats following intragastric administration of 10 mg asbestos 3 times/week for 10 weeks. Human studies are limited to the detection of fibers in body fluids which has not been associated with specific health effects. Other studies were performed on in vivo and in vitro test systems.

It is, therefore, evident that there are insufficient toxicological data on which to base a recommendation for a 1-day or 10-day HA for asbestos. In addition, it is also considered prudent not to derive an AADI, since the endpoint toxicity from inhaled asbestos exposure is carcinogenicity and the latent period for the cancer to appear from an occupational exposure of asbestos is in the magnitude of 20+ years.

Carcinogenic Effects

Inhalation animal studies have shown that amosite, anthophyllite, crocidolite and chrysotile have all produced lung tumors and mesotheliomas in laboratory animals. The first unequivocal data that showed a relationship between asbestos inhalation and lung malignancy in laboratory animals was that of Gross et al. (1967) who observed carcinomas in rats exposed to a mean concentration of 86 mg/m^3 chrysotile for 30 hours/week from the age of 6 weeks. From a total number of 72 rats surviving for 16 months or longer, 19 developed adenocarcinomas, 4 developed squamous cell carcinomas, and 1 developed a mesothelioma. Subsequent inhalation studies on animals by various investigators have shown the definite relationship between asbestos exposure and the incidence of lung cancer in animals. However, while all inhalation experiments focused on thoracic tumors, those of Wagner et al. (1974), Davis et al. (1978) and, to a limited extent, Gross et al. (1967) also included a search for tumors at extrathoracic sites. A limited number of these tumors were found by investigators; however, no association was specifically observed with asbestos exposure.

In animal populations, the majority of the experimental evidence suggests that chronic, high-level ingestion exposures to asbestos fibers failed to produce any definite, reproducible, organ-specific carcinogenic effect. This conclusion is based on the findings of 12 studies on two animal species, rat and hamster.

Some associations between specific cancer types and asbestos ingestion exposures have been made from studies on human populations. Specifically, cancers of the lung, stomach and pancreas have been implicated as possibly being associated with the ingestion of asbestos in water. This conclusion is based on a critical review of 14 epidemiological studies. Unfortunately, there is a large variability in the findings of these studies and, as discussed at length in Chapter VI, these studies suffer from severe limitations. The discrepant results may be due to differing asbestos exposures (fiber type, concentration, duration), confounding factors (occupation, personal habits), misclassification and others. Limitations are due to differing study designs and their underlying strengths, weaknesses and inherent biases, inability to gather historical exposure information, among others.

No individual carcinogenicity study or aggregation of carcinogenicity studies exist that would establish risk levels from the ingestion of asbestos because of these inconsistencies and limitations (Marsh, 1983). Instead, the studies performed (with their limitations and inconsistencies) provide information that should be considered in developing much needed future research.

Quantification of Carcinogenic Effects

For the quantification of carcinogenic effects, there should be available definite studies, either animal or human, characterizing the dose-response level of asbestos ingestion. However, the bulk of the experimental evidence indicates that long-term, high-level ingestion exposure to various types of asbestos fibers failed to produce any definite, reproducible, organ-specific carcinogenic effects. In epidemiological studies of the effects of asbestos in drinking water, a possible excess incidence of GI cancers were evaluated as were morbidity or mortality rates for some other cancers. The duration of exposure ranged from as little as 20 years (in Duluth) to more than 50 years (in Quebec); asbestos concentrations ranged from less than detectable limits to $1300x10^{6}$ fibers/ℓ.

The studies did not indicate consistent excesses of cancer. In Duluth, no consistent type of cancer in excess among residents was reported (Levy et al., 1976; Mason et al., 1974; Sigurdson et al., 1981). In Quebec, cancer mortality was evaluated in relation to asbestos in municipal water supplies. Some excess cancers observed in males were attributed to probable occupational exposure (Wigle, 1977; Toft et al., 1981). In Connecticut, tumor registry data indicated that there was no association between asbestos risk scores and GI tumor incidence (Harrington et al., 1978; Meigs et al., 1980). In San Francisco, there were inconsistent excesses of some cancers (Conforti et al., 1981; Kanarek et al., 1980; Tarter, 1981). In Puget Sound, a proportional incidence analysis that compared length of residence suggested an excess for some GI cancers (Polissar et al., 1982).

All of the above epidemiological studies had weaknesses. The most serious weakness evolved from the substantial problems in classifying exposure because population data rather than individual data were used. Errors in classification will tend to weaken any true association that may exist between asbestos in drinking water and health. Considering the problems in determining individual exposure, these studies cannot be taken as strong evidence that ingestion of drinking water containing asbestos fibers causes cancer.

However, occupational epidemiological studies have shown that occupational exposure to asbestos causes a marked increase in the incidence rates of lung cancer, pleural and peritoneal mesothelioma. The incidence rate of GI tract cancers in exposed workers is increased in some studies. The consistency of an increased cancer risk at extrathoracic sites and its magnitude, either in absolute (observed-expected deaths) or relative (observed/expected deaths) terms, was less for cancer at other sites than for lung cancer. As discussed earlier, 5 of 13 studies demonstrated the risk at a $p<0.05$ level of significance. A consistent relationship was observed between a greater GI cancer risk and an increased lung cancer risk in those studies where the overall lung cancer was elevated at the $p<0.05$ level of significance.

Extrapolation from Human Inhalation to Human Ingestion. The U.S. EPA (1980) and the NAS (1983) have extrapolated the results of cohort studies of populations occupationally exposed by inhalation in order to estimate the risk associated with the ingestion of asbestos in drinking water. The Ambient Water Quality Criteria Document (U.S. EPA, 1980) and the Drinking Water and Health report (NAS, 1983) consider much the same data of occupationally exposed workers with GI tract cancers, but use a slightly different method of calculating the "additional lifetime cancer risk of 1 in 100,000." The estimated levels that would result in increased lifetime cancer risks of 10^{-5}, 10^{-6} and 10^{-7} calculated by the U.S. EPA (1980) are 300,000 fibers/ℓ, 30,000 fibers/ℓ and 3000 fibers/ℓ, respectively. Corresponding numbers for males calculated by the NAS are 110,000 fibers/ℓ, 11,000 fibers/ℓ and 1100 fibers/ℓ. The more restrictive NAS levels arise mainly from two different assumptions than those used by the U.S. EPA.

1. The NAS assumed that 30% of the inhaled fibers were subsequently swallowed, where the U.S. EPA assumed that 100% would be eventually cleared and ingested.
2. The NAS assumed a conversion factor of 50 for optical microscopy to transmission electron microscopy, where the U.S. EPA assumed a factor of 200.

The above extrapolation of the results of cohort studies of occupationally exposed populations to estimate the risk associated with the ingestion of asbestos are based on the following assumptions:

1. Inhaled fibers are swallowed and are responsible for the increased risk of GI cancer and peritoneal mesothelioma in persons occupationally exposed to asbestos.

2. The number of fibers 5 μm or longer detected by optical microscopy is ~1/200th (or ~1/50th) of the amount of fibers of all lengths that can be detected by electron microscopy.

3. The fiber size distribution is the same in occupational air and drinking water samples.

4. Exposure to waterborne asbestos is over a 70-year period.

The assumption "inhaled fibers are swallowed and are responsible for the increased risk of GI cancer in persons..." raises some questions regarding its validity in view of the following facts:

1. Inconclusive evidence was found from toxicological studies conducted with laboratory animals in determining its carcinogenic or noncarcinogenic potential. Early studies were inconclusive because of shortcomings in study design. Until recently, extensive investigations had revealed no statistically significant differences between the GI tumor incidence in treated and control groups of animals. However, data from the NTP (1984) rat diet study with 1% intermediate range chrysotile fibers have shown a significant increase in adenomatous polyps of the large intestine.

2. Disagreements were reported among the Chronic Hazard Advisory Panel on Asbestos (CHAP) in its report to the U.S. Consumer Products Safety Commission (1983) concerning other forms of cancer:

> "Lung cancer and mesothelioma constitute the majority of asbestos produced cancers. The association of these malignancies with asbestos exposure is firmly established. Some other forms of cancer, particularly digestive tract, oral, pharyngeal, laryngeal, and kidney, have, in some large studies, been found to be increased; there are disagreements among Panel members as to the strength of the evidence associating this group of cancers with asbestos exposures."

3. The NAS (1983) has also reviewed a number of epidemiological studies of GI cancer associated with occupational exposure to asbestos. They note that the reported relative risks, while significant, are not very large and that several other studies did not detect any increased GI cancer risk. After reviewing these studies and the reports of several authors and other committees, they agree with the Advisory Committee on Asbestos (1979), the International Agency for Research on Cancer (IARC, 1977) and Miller (1978), "that the demonstrated association of asbestos exposure and GI tract cancer is most likely one of cause and effect."

The U.S. EPA concurs with the position of the NAS (1983), Advisory Committee on Asbestos (1979), IARC (1977) and Miller (1978) and adds that lung cancer might also be caused by ingested asbestos that can transmigrate through the GI wall. In the asbestos contaminated drinking water study in the San Francisco Bay area, lung cancer in males was found to be strongly associated with the asbestos in the water supply, even after adjustments for selection bias (Kanarek et al., 1980). At this time, however, it is felt that such data do not support a quantitative estimate of risk from lung cancer due to ingested asbestos.

Extrapolation from Animal Ingestion to Human Ingestion. While the evidence of an asbestos carcinogenic effect by ingestion studies is limited, the establishment of asbestos as both a human and animal carcinogen by inhalation is certain. Furthermore, the transmigration of asbestos through the GI wall is also established by the preponderance of evidence (Table III-1). As such, this section will present an estimate of upper-limit risk for asbestos by ingestion. The data base chosen to calculate the estimate is from a draft of the NTP (1984) ingestion study of chrysotile short range

(98% < 10 µm) and intermediate range (65% > 10 µm with ~14% > 100 µm) fibers (counts by TEM). The results of the NTP (1984) study showed no evidence of carcinogenicity for the short range fibers in either male or female rats, and no evidence of carcinogenicity for the intermediate range fibers in the female rats. However, for the male rats ingesting the intermediate range fibers at 1% of the diet ad lib (or 10,000 mg/kg), benign epithelial neoplasms (adenomatous polyps) were observed in the large intestine at the incidence of 9/250 (3.6%).

> "Although not statistically significant (p=0.08) compared with concurrent controls (0/85), the incidence of these neoplasms was highly significant (p=0.003) when compared with the incidence of epithelial neoplasms (benign and malignant combined) of the large intestine in the pooled control groups (male) of all the NTP oral asbestos lifetime studies (3/524, 0.6%)" (NTP, 1984).

Based on these findings, the NTP claimed there was "some" evidence of carcinogenicity in male rats exposed to intermediate range chrysotile fibers.

In order to estimate a unit risk in drinking water for asbestos, an assumption must first be made that the asbestos in the dry diet would have the same effect as asbestos in water. In order to establish dose it is assumed that a rat consumes ~5% of its body weight/day. The average body weight of this group of male rats at 52 weeks was ~0.38 kg; this will be taken as the weight of the average rat. Thus, the daily dose is

$$(0.38 \text{ kg} \times 0.05)\ (10{,}000 \text{ mg/kg of diet}) = 190 \text{ mg (or } 500 \text{ mg/kg)}.$$

Based on measurements by TEM performed at the Illinois Institute of Technology Research Institute, the fiber counts/g were 0.1291×10^{12} (NTP, 1984) (or ~0.129×10^9 f/mg) with a median fiber aspect ratio (length divided by diameter) of 8.435. Changing the daily dose to the number of fibers yields

$$500 \text{ mg/kg} \times 0.129 \times 10^9 \text{ f/mg} = 6.45 \times 10^{10} \text{ f/kg}.$$

In order to determine human equivalent dose, the U.S. EPA procedure has been to assume dosage equivalency on a dose/surface area basis. This is roughly equal to equivalency on a dose/(body weight)$^{2/3}$. Thus, equivalent human dosage for a 70 kg human is

$$(6.45 \times 10^{10} \text{ f/kg})/(70/0.380)^{1/3} = 1.13 \times 10^{10} \text{ f/kg bw}.$$

Since a 70 kg human drinks ~2 ℓ of water/day, this dose, in terms of drinking water, becomes

$$1.13 \times 10^{10} \text{ f/kg} \times 70 \text{ kg}/2 \text{ ℓ} = 4.0 \times 10^{11} \text{ f/ℓ}.$$

Since there is only a control and one dose level the usual linearized multistage model is reduced to a single dose or one-hit model. The maximum likelihood estimate (mle) of potency* is

$$q_1 = -\ln \frac{(1-P_t)}{(1-P_c)} /d = -\ln [(1 - 0.036)/(1 - 0.006)]/4.0 \times 10^{11} \text{ f/ℓ}$$

$$= 7.7 \times 10^{-14} (\text{f/ℓ})^{-1}$$

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*The potency and concentration estimates given in this section (mle and 95% confidence limits) are statistical estimates only under the assumption that the one-hit model is correct.

with a 95% upper-limit potency

$$q_1^* = 1.4 \times 10^{-13}\ (f/\ell)^{-1}.$$

For a lifetime individual risk of 10^{-6}, the maximum likelihood estimate of concentration is 1.3×10^{7} f/ℓ with a 95% lower limit of 7.1×10^{6} f/ℓ for individual lifetime risk of 10^{-5} to 10^{-7} the corresponding estimates are given below.

Lifetime Individual Risk	Maximum Likelihood Estimate of Fiber Concentration (f/ℓ)	95% Lower Limit of Fiber Concentration (f/ℓ)
10^{-5}	1.3×10^{8}	7.1×10^{7}
10^{-6}	1.3×10^{7}	7.1×10^{6}
10^{-7}	1.3×10^{6}	7.1×10^{5}

The above levels are calculated from the IR chrysotile fiber study. As such, the levels are much more restrictive than they would have been had they been calculated from the SR chrysotile fiber study. The SR study showed no effects with 50 times the number of fibers as the IR study. If the data from the SR study had been included with the data from the IR study using only the number of fibers, the resulting levels would have been at least 10 times higher (i.e., less restrictive) than the levels given above.

The IR study itself contained shorter fibers (although still within the defined IR) which in the SR study were shown to be noncarcinogenic. If these shorter fiber counts had been eliminated from the positive IR fiber study, the resulting levels would have been lower than those listed above by a factor of ~2.5.

Conclusions

1. Although it is not possible to conclude with certainty that ingested asbestos fibers do not cross the intact GI tract wall, the weight of evidence is in favor of this occurrence.

2. By inhalation, asbestos has been shown to cause lung cancer and pleural mesothelioma in humans and animals. It is also positively associated with GI tract cancer and peritoneal mesothelioma in several human occupational studies. By the ingestion route the results are less certain. In humans, environmental drinking water studies in San Francisco and Washington State have been associated with increased GI cancer levels. In San Francisco, lung cancer has also been associated with asbestos in drinking water. However, by their nature, these studies were designed to detect overt differences and not to define cause and effects. In animals, only a recent NTP (1984) study has shown a small but significant increase in adenomatous polyps of the large intestine in the male rat exposed to intermediate range chrysotile fibers.

3. The available information on the risk of developing GI cancer associated with the ingestion of asbestos from drinking water is limited. Using the NTP (1984) 1% intermediate range (IR) chrysotile fiber diet study in male rats, individual lifetime estimates of risk can be made. However, they possess a wide range of uncertainties and the estimates are applicable only for IR chrysotile fibers. The criteria levels derived are 430

times greater (less restrictive) than those derived using the inhalation occupational exposure data (U.S. EPA, 1980) specific for amosite and chrysotile fibers.

Special Considerations

High-Risk Subpopulations. The effects of ingested asbestos on human populations have been examined based on the response of large exposed groups. To date, there have been no studies that have attempted to isolate or quantify the effects of asbestos ingestion on any specific subgroup within an exposed subpopulation to demonstrate increased susceptibility to adverse effects.

Multiple Pollutant Exposures. Some data are available from in vitro experimentation suggesting an enhancement of the effects of the carcinogen BaP on asbestos fibers (Chapter VII). The impact of these effects for ingested asbestos is not clear.

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APPENDIX

Assessment of Asbestos Studies with Respect to Fiber Type and Size

Introduction

It is well known that asbestos is not one but a family of fibrous minerals, each of which has distinctive physical and chemical characteristics. Minerals from various parts of the world and geologic formations often have dissimilar physical properties, even though they are classified under a specific mineralogic type. These differences are relevant to the understanding of the effects of asbestos on health, since the characteristics of the fibers have been fully defined in only a few experimental studies. The problem of evaluating the effects of different types of asbestos on health is compounded by the common practice of custom blending various minerals for a specific industrial application, and different analytical techniques for measurements of asbestos (mass vs. fibers), etc.

The major pathologic effects of asbestos result from the inhalation of fibers suspended in the air. The occurrence of disease is influenced by the type of mineral and the dimensions of the fibers that constitute it, as well as by the concentration of fibers and the duration of exposure.

When nonfibrous compact dust particles are inhaled, the ones greater than ~5 μm in diameter are generally trapped in the nasal passage before reaching the respiratory system (Walton, 1982). However, the inhaled fibers align themselves parallel to the airways and act as spheres of approximately "equivalent" diameter (Gross, 1981; Timbrell et al., 1970). The equivalent or aerodynamic diameter of a particle is defined as the diameter of a sphere with a density of 1 g/cm³ that has the same falling speed as the particle. There is no sharp cutoff of particle sizes determining their deposition site (Brain and Valberg, 1979).

Inhalation of Asbestos by Fiber Type

In occupational circumstances, the current method of quantitating asbestos air concentrations allows only for the enumeration of all fibers longer than 5 μm collected on a specified area of filter, utilizing phase-contract light microscopy (NIOSH, 1972). Such instrumentation does not allow for the identification of the fibers according to mineral type or size.

It is a well established fact that inhalation exposure of asbestos is associated with increased risks of lung tumors (bronchogenic carcinoma and peripheral adenocarcinoma), pleural and peritoneal mesothelioma, interstitial pulmonary fibrosis (asbestosis), pleural thickening and possible other tumors, including those of the GI tract and kidney. Investigators have induced lung tumors, mesotheliomas and fibrosis after administration of asbestos of animals. In some of these experimental studies in animals, the investigators have provided a description of the size and types of fibers used. For example, Lee et al. (1981) have shown that the inhalation of amosite (AM), fiber glass (FG) and potassium octatinate (Fybex) in rats and hamsters caused adenoma, carcinoma and mesothelioma over the 3 months of exposure. The reported length of Fybex fiber was >5 μm (Table A-1).

Table A-2 shows the occurrence of mesotheliomas appearing in rodents after injection of asbestiform fibers. This injection technique has been used most frequently in reported studies because of its reproducibility

TABLE A-1

Respiratory Tract Tumors in Rodents After Inhalation of Asbestos and Other Asbestiform Fibers*

Fiber Type	(No. of Tumors/ No. of Animals	Animal	Tumor Types	Reference
AM, FG (fine), Fybex (>5 μm length), PKT	Experiment 1: AM (3/16), FG (2/19), Fybex (1/21) in rats, Fybex (1/12 in hamsters	Rat guinea pig, hamster	adenoma, carcinoma, mesothelioma	Lee et al., 1981
	Experiment 2: Fybex (3/25), Fybex (1/19), in rats, Fybex (2/16) in hamsters			
Alumina (medium length, 35-62 μm; diameter 1-5 μm) vs. CH (UICC)	Alumina = 0/60 CH = 5/38	rat	adenoma, squamous cell, adenocarcinoma	Piggott et al., 1981

*Source: Adapted from NAS, 1984

AM = Amosite; FG = fiberglass; Fybex = potassium octantinate, PKT = pigmentary potassium titanate, CH (UICC) = chrysotile (International Institute Against Cancer)

TABLE A-2

Mesotheliomas in Rodents Appearing after Injection of Asbestiform Fibers*

Mode of Administration	Dose (mg)	(No. of Tumors/No of Animals) or Percent Tumors by Fiber Exposure	Animal	Reference
Intrapleural or intrathoracic	1 time CR = 1, 10, 40 mg on	CH (15/30), AM (15/30), CR (14/30), milled CR (8/30), FG (1-25 μm diameter, 1/30), FG (0.06-3 μm diameter, 4/60), CR (at 1 mg, 2/40; at 10 mg, 11/40), pledget alone (0/40)	rat	Stanton and Wrench, 1972
	40 on glass pledget	17 samples of FG tested; greatest tumor incidence observed for FG >8 μm length, <1.5 μm diameter	rat	Stanton et al., 1977
	40, 1 time	CR, CH, FG, alliminum oxide all <5 μm diameter, >50% tumors	rat	Stanton and Layard, 1978
	40, 1 time	Most fibers ≤0.25 μm diameter, >8 μm length were tumorigenic, but induction also observed for fibers <1.5 μm diameter, >4 μm length; 72 experiments	rat	Stanton et al., 1981
	0.5, 1, 2, 4, 8 (SFCH, CR); rest, 20, 1 time	Dose response: Tumors observed with SFCH, CH, milled CH, AM, AN, CR, brucite ceramic fiber, barium sulfate, FG, glass powder, aluminum oxide. Tumors were induced with nonfibrous materials, but more were seen with fibers >10 μm length, <5 μm diameter	rat	Wagner et al., 1973
	20, 1 time	CH (45%); leached (0-3%); CR (54%); leached fibers were shorter, thicker and there were fewer per unit weight	rat	Monchaux et al., 1981

TABLE A-2 (cont.)

Mode of Administration	Dose (mg)	(No. of Tumors/No of Animals) or Percent Tumors by Fiber Exposure	Animal	Reference
	1, 10, 25	CR: at 1 mg (2/50), at 10 mg (10/50); AM: at 10 mg (3/50); CH: at 1 mg (0/50), at 10 mg (4/50), at 25 mg (9/50); AM: at 1 mg (0/50), at 10 mg (4/50); talc at 25 mg (0/50), control 0/100); milled CH at 25 mg (<0.37 μm length, 0.07 μm diameter (0/150); fibrous nemalite at 25 mg (0/50); silicon dioxide at 10 mg (4/40), FG (50 μm diameter, 0/50)	hamster	Smith and Hubert, 1974
	25, 1 time	Group 1: FG 0.1 μm diameter, 82% >20 μm length (5/60); Group 2: FG 0.3 μm diameter, 46% >20 μm length (2/60); Group 3: FG 1.23 μm diameter, 34% >20 μm (2/60); none in three groups of FG where 2% >10 μm length	hamster	Smith et al., 1980
Intraperitoneal	0.5, 2, 5, 10	Diversity of mineral fibers ≤ 20 μm diameter, <0.25 μm length; GF induction of tumors reduced with hydrogen chloride and NaOH treatment	rat	Pott et al.,

*Source: Adapted from NAS, 1984

CH = Chrysotile; CR = crocidolite; AM = amosite; FG = fibrous glass; GF = glass fiber; SFCH = superfine chrysotile

(NAS, 1984). Stanton et al. (1977, 1981) reported that tumor incidence was greatest for fibrous glass >8 μm in length. Wagner et al. (1973) observed in their experiments that fibers >10 μm in length were more tumorgenic than nonfibrous materials. From the data presented in Table A-2, it may be stated that exposure to long (>8 μm) fibers results in the appearance of mesotheliomas. Nonfibrous particles, including cleavage fragments, do not generally cause tumors.

Fibrosis, associated with asbestos and asbestiform fibers, has been experimentally produced in various animal studies. Table A-3 shows those studies for which fiber types have been reported by the investigators. The important features of these experiments can be summarized by stating that inhalation and pleural injection studies implicate the increased fibrogenic potential of longer (>10 μm) fibers of both asbestos and fibrous glass.

Fredricks (1979) also provides some interesting data concerning morphological aspects, namely the size and shape of fiber content in human lung dusts. The author observed that most of the fibers in the lung of the one asbestos worker were shorter than 20 μm in length and thinner than 1 μm. However, the majority of fibers in the samples of the analyzed groups (normal, mesothelioma cases and asbestosis plus mesothelioma) were shorter than 30 μm and thinner than 2 μm, the longest fibers were found to be 180 μm.

In summary, even though the interpretation of the experimental results of many asbestos and asbestiform studies regarding pathogenicity of various

TABLE A-3

Development of Fibrosis in Animals after Inhalation or Intratracheal Instillation of Asbestos and Other Asbestiform Fibers[a]

Mode of Administration	Fiber Type	Concentration (mg/m³)[b]	Animal	Latency (months)	Observations	Reference
Inhalation, instillation	GW 20-50 μm length and short fibers	ND	guinea pig	ND	No fibrosis	Schepers and Delahant, 1955
	CH, CR, AN, AM, TR, brucite, all long (20-50 μm) vs. short (<5 μm)	ND ≤ 3 years	rat, guinea pig, mouse, cat, dog	16 (guinea pig) 14 cat	Fibrous reaction: Guinuea pig > rabbit = cat = rat > mouse and dog. Long CR fibers: Fibrosis; long AM, CR, brucite → peribronchiolitis; long TR → bronchiolar fibrosis; AN → no fibrosis; no fibrosis with short fibers.	Vorwald et al., 1951
Combined inhalation and instillation	FG (0.5 μm diameter, 5-20 μm length)	100 24 months	rat, hamster	NA	Mild macrophage infiltration without fibrosis.	Gross et al., 1970, 1974
Instillation	Sized CR, CH, FG, synthetic fluoroamphibole	3-25 2-6 times	guinea pig	24	Minimal peribronchiolar fibrosis only with fibers >10 μm length.	Kuschner and Wright, 1976

[a] Source: Adapted from NAS, 1984

[b] Applied to inhalation exposures. Dose expressed differently for other types of exposure.

CH = Chrysotile; CR = crocidolite; AN = anthophyllite; AM = amosite; FG = fibrous glass; TR = tremolite; GW = glass wool

ND = no details given in report; NA = not applicable fiber types is complicated (because only the mass of asbestos administered was mentioned), the data presented in the preceding section suggest the following:

1. Respiratory tract tumors are observed in rats and hamsters following inhalation exposure to Fybex (potassium octatinate) >5 μm length (Table A-1) (Lee et al., 1981).
2. Inhalation exposure to long (>10 μm) fibers results in the appearance of mesotheliomas, (rats). Nonfibrous particles, including cleavage fragments, do not generally cause tumors.
3. Inhalation and plueral injection studies implicate the increased fibrogenic potential of longer (>10 μm) fibers of both asbestos and fibrous glass, (rats).

Ingestion of Asbestos by Fiber Type

There are few ingestion studies in which mineral and fiber characterization of asbestos fibers are reported (Table A-4). The results of bioassays of amosite (median length 4.37 μm, range 0.85-995 μm), and chrysotile short-range (SR, median length 0.66 μm, range 0.088-51.1) or intermediate-range (IR, median length 0.82 μm, range 0.104-783) did not demonstrate any carcinogenicity in hamsters when ingested over the lifetime period (McConnell et al., 1983b). In another ingestion study in animals, McConnell et al. (1983a) demonstrated that amosite asbestos with a median length of 4.37 μm (range 0.85-995) was not carcinogenic when ingested at a level of 1% in the diet by male and female rats.

Recently the NTP (1984, draft) has reported the results of a study on the carcinogenic potential of the ingestion of chrysolite short-range (98% <10 μm) and intermediate-range (65% >10 μm with 14% >100 μm) fibers. The results of the study showed no evidence of carcinogenicity for the SR fibers in either male or female rats, and no evidence of carcinogenicity for

TABLE A-4

Digestive Tract Tumors in Rodents after Administration of 1% in Diet of Abestos

Fiber Type	Dose in Diet Lifetime (%)	Fiber Size Length/Diameter		Digestive Tract Tumor		Animal	Reference
		Short-Range (μm)	Intermediate-Range (μm)	Short-Range (μm)	Intermediate-Range (μm)		
Chrysotile	1	0.088-51.1/ 0.019-1.57	0.104-783/ 0.019-11.5	ND	ND	hamster	McConnell et al., 1983
Amosite	1	-	0.85-995/ 0.064-12.4	-	ND	hamster	McConnell et al., 1983
Amosite	1	-	0.85-995/ 0.064-12.4	-	ND	rat	McConnell et al., 1983
Chrysotile	1	0.088-51.1/ 0.019-1.67	0.104-783.4/ 0.019-11.5	ND	Not detected in females. Benign epithelial nodules in 9/250 males	rat	NTP (1984, draft)

ND = Not detected

the IR fibers in the female rats. However, for the male rats ingesting the intermediate-range fibers at 1% of the diet, benign epithelial neoplasms (adenomatous polyps) were observed in the large intestine at the incidence of 9/250. Based on these findings, the NTP concluded that there was some evidence of carcinogenicity in male rats exposed to IR chrysotile fibers.

In summary, the results of bioassays of amosite asbestos (median length of 4.37 μm) and chrysotile asbestos (<10 μm in length) do not show carcinogenic potential in hamsters and rats when fed at 1% in the diet over the lifetime period. However, there is some evidence of carcinogenic potential associated with chrysotile asbestos >10 μm in length, in male rats over the lifetime exposure.

Epidemiologic Asbestos Ingestion Studies by Fiber Type

Marsh (1983) reviewed and evaluated epidemiological studies of ingested asbestos conducted in five areas of the United States and Canada for the definitiveness and applicability regarding the development of ambient water quality standards. Several methodologic weaknesses and limitations were found in each study, leading to the determination that no individual study or aggregation of studies exist that would establish risk levels from ingested asbestos. The author considered that one of the factors that may have attributed to considerable discrepancies might have been the characteristic of asbestos exposures in drinking water in various study populations. The type of asbestos and other pertinent information are provided in Table A-5. It is seen from the table that the chrysotile asbestos was present in water supplies of 4 of the 5 study populations.

TABLE A-5

Characterisitics of Asbestos Exposures in Drinking Water in Various Study Populations

Characteristic	Duluth, MN	Connecticut	Quebec	Bay Area, CA	Utah	Puget Sound, WA
Type of asbestos	amphibole	chrysotile	chrysotile	chrysotile	chrysotile	chrysotile
Number of fibers/ℓ	$1.0-30.0\times10^6$	BDL-0.7×10^6	$1.1-1300\times10^6$	$0.025-35\times10^6$	NA	$7.3-206.5\times10^6$
Population exposed	100,000	576,800	420,000	3,000,000	24,000	200,000
Maximum duration of exposure, year	15-20	23-44	>50	>40	20-30	>40

BDL = Below detectable limit

NA = Not available

Millette et al. (1980) in a review of the results of >1500 asbestos analyses from water supplies suggest that the average length of chrysotile fibers found in an asbestos cement distribution system was 4 µm, while the average fiber length of chrysotile fibers contributed to a water supply by natural erosion was 1 µm. Some size characteristics of asbestos fibers found in various water supplies are given in Table A-6.

In summary, an attempt is made to assess the size characteristics of asbestos/asbestiform fibers and their pathologic effects of of various exposures. This report has delineated the various pathologic effects of asbestos/asbestiform fibers associated with inhalation, ingestion exposure and pleural injection. It is recognized that these studies were not carried out under rigid experimental conditions, and yet, even with these guidelines, the results of the experiments conclude that asbestos fiber >10 µm plays a significant role in producing various effects.

Discussion

Lee et al. (1981) have shown that the inhalation of amosite, fiberglass and potassium octatinate in rats and hamsters caused adenoma, carcinoma and mesothelioma. The reported length of potassium octatinate fiber was >5 µm.

In other studies, Stanton et al. (1977, 1981) reported that tumor incidence in animals was greatest for fibrous glass >8 µm in length. Similarly, Wagner et al. (1973) also observed in their experiments that fibers >10 µm in length were more tumorgenic than nonfibrous material in animals (rats).

TABLE 6

Some Size Characteristics of Asbestos Fibers Found in Various Water Supplies

Source	Type of Fiber	Number of Fibers (µm)	Average Length (µm)	Average Width (µm)	Average Aspect Ratio*	Maximum Length Found (µm)
Reservoir with natural erosion (WA)	chrysotile	289	0.8	0.034	25:1	3
Reservoir with natural erosion (CA)	chrysotile	644	1.3	0.04	39:1	10
Cistern with asbestos tile roof (VI)	chrysotile	342	2.3	0.04	62:1	25
Distribution sites from five asbestos cement pipe system (SC, PA, FL)	chrysotile	1440	4.3	0.044	121:1	80
Lake Superior (MN)	amphibole	468	1.5	0.18	11:1	14

*Length/width

Data concerning fiber size in human lung dust in asbestos exposed workers (Fredrick, 1979) showed that the majority of fibers in the samples of the analyzed groups were in the range of 10-30 μm in length.

Lifetime asbestos ingestion bioassays for carcinogenicity in animals by McConnell et al. (1983a,b) and NTP (1984, draft) provide some interesting information on the asbestos fiber size and its carcinogenicity in animals. McConnell et al. (1983b) reported no evidence of carcinogenicity of the GI tract in hamsters following administration of diet containing 1% amosite (median length 4.37 μm) or chrysotile asbestos consisting of short-range (median length 0.66 μm) or intermediate-range (median length 0.82 μm) fibers. The investigators also reported that ingestion of amosite consisting of a median length of 4.37 μm resulted in no GI tract carcinogenicity in rats.

In a recent report, the NTP (1984, draft) showed that intermediate-range chrysotile asbestos consisting of median length fibers of 0.82 μm (65% >10 μm; 14% ≥100 μm) was associated with causing benign epithelial neoplasms (adenomatous polyps) in the large intestine of male rats when fed at 1% in the diet. The short-range chrysotile asbestos (median length 0.66 μm; 98% <10 μm in length) had not effect on male or female rats.

Implication of the assessment of asbestos fibers >10 μm in length being responsible for observed carcinogenicity in animals and humans leads to:

1. The explanation why there was no clear evidence of GI tract cancer observed in the populations drinking water containing asbestos in the epidemiological ingestion studies.

2. The determination of excess lifetime cancer risk, if any, from the ingestion of chrysotile fibers >10 μm in length from drinking water contaminated with asbestos.

The reasons for the lack of increase in the GI tract cancer in the populations drinking water containing asbestos (epidemiological studies) may be that the fibers present in these water supplies were <10 μm in length. In support of this argument, the Marsh (1983) review of 13 epidemiological studies provides the asbestos "type" present in these water supplies and Millette et al. (1980) provide the size of asbestos fiber present in some of those water supplies of epidemiological ingestion studies. Marsh (1983) has stated that the asbestos "type" present in the water supplies of 4 out of 5 areas was chrysotile asbestos. Millette et al. (1980) in their review of results of >1500 asbestos analyses of water supplies of various areas (e.g., California, Washington, etc.), demonstrate that the average length of chrysotile asbestos in the asbestos cement distribution system was 4 μm, while the average fiber length of chrysotile asbestos contributed to a water supply by natural erosion was 1 μm. Therefore, these arguments strongly suggest that the lack of increase in GI tract cancer in the populations drinking water containing asbestos might be due to the majority of chrysotile asbestos being well below 10 μm in length.

With regard to determining excess lifetime cancer risk from ingestion of chrysotile asbestos >10 μm in length, the evidence of asbestos carcinogenicity of GI tract is limited. As such, the data base chosen to calculate the estimate of risk (GI tract cancer) by ingestion is from a draft of the

NTP (1984) ingestion study of intermediate-range chrysotile asbestos >10 μm in length. Using this study, the estimated levels which would result in increased lifetime cancer risk (fibers/ℓ) of 10^{-5}, 10^{-6} and 10^{-7} are: 7.1×10^7, 7.1×10^6 and 7.1×10^5 fibers/ℓ, respectively.

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